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ARCHIVES OF SURGERY

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BENIGN AND MALIGNANT GROWTHS OF THE NASOPHARYNX AND THEIR TREATMENT WITH RADIUM *

S. J. CROWE, M.D. AND JOHN W. BAYLOR, M.D.

BALTIMORE

The primary object of this article is to report our experiences with the use of radium as a therapeutic agent in nasopharyngeal growths; but we also wish to emphasize the fact that here, as elsewhere in the body, the growth must be recognized during the earliest stages of its development in order to improve materially our present therapeutic results—whether the method of treatment employed is operative, the actual cautery or irradiation.

Our results with the radium treatment of lymphosarcoma of the nasopharynx are not good, although this variety of sarcoma disappears locally after irradiation more rapidly than does any other type of tumor with which we are familiar. One possible explanation for this unsatisfactory clinical result is that the earliest symptoms of lymphosarcoma in the nasopharynx are difficulty in breathing through the nose and eustachian tube obstruction, and that these symptoms are usually treated without recognition of the underlying cause until the growth has become diffused throughout the body. We believe that it would be a wise precaution to treat with radium every adult patient that has a localized hypertrophy of the lymphoid tissue limited to the nasopharynx, rather than to remove this hypertrophied tissue with a curet (Case 1). If it were possible to make a definite differential diagnosis between lymphosarcoma and benign hypertrophy from the microscopic appearance of a small fragment of the growth, the excision of a piece for diagnosis might be justifiable; but, unfortunately, a differential diagnosis is often not possible unless the section includes a large portion of the tumor.

When a localized, hard, submucous swelling is discovered in the nasopharynx, or a circumscribed lesion is seen on the mucous membrane that suggests an early carcinoma, thorough surgical extirpation, without preliminary excision for microscopic diagnosis, is the method most likely to result in a cure. In the later stages of carcinoma of the naso-

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pharynx, surgical removal is hopeless, and although irradiation will greatly ameliorate the symptoms and will occasionally remove the local growth, a cure is rarely possible on account of the metastases.

The tumors that arise in the posterior half of the nasal cavities and in the nasopharynx are particularly suitable for the study of radium as a therapeutic agent. The malignant growths that arise in these areas are as a rule recognized so late that complete operative removal is not possible, and many of the benign growths are so vascular that removal would necessitate an extensive and deforming operation. It is in this type of benign tumor that we have had the best results with radium; but the disappearance or marked decrease in size of the local growth in many of the malignant tumors has led us to believe that thorough irradiation at an early stage of their development would produce more favorable results.

When a malignant growth is accessible and can be completely removed without endangering the patient's life, we do not believe it advisable to jeopardize the chances of recovery by first trying radium or roentgen-ray therapy; but in many of the cases that we are reporting the growth was so extensive that it seemed justifiable to employ radium alone.

The clinical diagnosis in many of our cases was supplemented by the microscopic study of a small piece of the growth. The classification of the tumor may be incorrect, since it is often impossible to decide from the histologic appearance of a small fragment of tumor whether the growth is a carcinoma or a sarcoma. It is also difficult to classify the various types of sarcoma that occur in the nasopharynx, and, without the clinical findings or a large section of the tumor, it may be impossible to determine whether the growth is an angioma or an angiosarcoma, a round-cell sarcoma or a very cellular fibroma. This is due in part to the fact that only a small fragment of the tumor is removed for diagnosis and this fragment comes from the surface of the growth; but the difficulties of microscopic diagnosis are also increased by the inflammatory reactions that are so common in tumors of the upper air passages.

Clinically, it is not so important to determine whether the growth is a carcinoma, a sarcoma, an angioma or a fibroma. They all tend to invade the accessory nasal sinuses, the orbit and the intracranial cavity, and for surgical therapy one type is as inaccessible as another. It is desirable, however, to know what types of tumor respond most readily to radium, and, for this reason, we have excised bits of tumor in the majority of our cases.

Before discussing the details of our cases we will review briefly the various types of new growth that occur in the nose and nasopharynx, together with the signs and symptoms that lead to their recognition at an early stage of their development.

NASAL POLYPS

The polyp is the most prevalent type of tumor in the nasal passages. Ewing [1] describes it as a pseudoneoplasm of inflammatory origin that is probably always benign; but Heymann [2] reports three cases in which a polyp has become malignant. This is an important point. It is the general concensus of opinion that a nasal polyp itself does not become transformed into a malignant tumor, but that the polyp appears in certain cases as a result of a deep-seated primary malignant growth under the mucous membrane. Infection is the etiologic factor of the nasal polyp in about 95 per cent. of the cases; but the possibility of an underlying growth must always be considered. There is at present a patient in the Johns Hopkins Hospital whose case well illustrates this point:

A white girl, aged 16 years, was admitted with an extensive bilateral destruction of the superior maxilla and a large defect in the hard palate. The history dates from an abscessed upper molar tooth, one year previously, and suggests an osteomyelitis. The painless course of the disease and the extensive destruction of bone suggest syphilis. Aside from the defect in the hard palate, the most prominent features on examination were: (1) Large myxomatous polyps filled the nasal cavities and nasopharynx. (2) All of the upper teeth were swaying in their sockets, and the roentgenogram revealed destruction of the entire alveolar process on both sides.

The Wassermann reaction of the patient and that of her mother were both negative, and intravenous therapy did not improve the local condition. We have never seen nasal polyps in association with a tertiary lesion in the nose or hard palate. The polyps in this girl were removed on two occasions. There was nothing unusual in their microscopic appearance, and the true nature of the malady was recognized only when a piece of the mucous membrane at the point of attachment of a polyp showed definite carcinoma.

Histologically, there are three types of nasal polyp: [1] (1) The fibroma edematoides simplex is made up of edematous connective tissue and fibroblasts. The epithelial covering may be ciliated, transitional or squamous. There is usually an accumulation of round cells under the surface epithelium and around the blood vessels. The edema is due to an albuminous transudate, with traces of mucin. (2) The adenofibroma edematoides often shows a pronounced hyperplasia of the surface epithelium and a large number of mucous glands, but the microscopic appearance rarely suggests a neoplasm. (3) The fibroma edematoides cysticum may be mistaken for a true myxoma. The clinical course and prognosis, however, are very different in these two

1. Ewing, James: Neoplastic Diseases, a Treatise on Tumors, Ed. 2, Philadelphia, W. B. Saunders Company, 1922 p. 80.

2. Heymann, P.: Die Gutartigen Geschwülste der Nase, Handb. d. Laryngol. u. Rhinol. **3**:829-830, 1900.

conditions. The fibroma edematoides cysticum is a benign polypoid growth and owes its appearance to the occlusion of alveoli and ducts of the mucous glands, while the true myxoma is a tumor that invades bone. Either of these conditions may arise in the ethmoidal region. The former is due to a primary infection in the accessory nasal sinuses and does not invade, while the latter is a neoplasm that invades the intracranial cavity or orbit.

The choanal polyp is a firm cellular tumor that arises from the mucous membrane of the maxillary or sphenoidal sinuses as the result of a low-grade chronic infection. This polyp differs from the types mentioned above only in its location and size. It grows through the natural orifices of the sinus and extends backward into the nasopharynx. Zarniko observed bone formation and marked hyperplasia of epithelium in a choanal polyp. Although these choanal polyps may fill up the entire nasopharynx, they do not adhere to the walls of the nasopharynx and soft palate as do the fibromas. A careful nasal examination will usually disclose the pedicle of the tumor coming from one of the accessory nasal sinuses. If the pedicle is divided, the growth will drop into the mouth. Simple division of the pedicle, however, will not prevent a recurrence; the mucous membrane from which the growth arises must be removed.

None of the various types of polypoid growths that occur in the nose or nasopharynx has a rich blood supply, and excessive bleeding following the removal of a polyp always suggests that the primary cause may be a malignant growth instead of an infection.

Irradiation has but little influence on the size or growth of polypoid or myxomatous tissue. We have never implanted either radium or its emanations into a nasal polyp; but we have repeatedly irradiated heavily both intranasally and externally without curing the polypoid condition.

H. R. Lyons [3] of the Mayo Clinic, however, believes that radium may be used to advantage in the treatment of myxomatous nasal polyps. He first removes the polyps, together with the mucous membrane from which they arise, and from three to six days later applies radium directly in the wound. He uses a 50 mg. tube enclosed in a silver capsule and covered with a sterile rubber finger-cot, and leaves it in place for two hours. The polyps may recur within a month after the treatment; but on microscopic examination they are found to contain more fibrous tissue than did the original polyps. A second operation, followed by a second irradiation will usually result in a cure. No burns

3. Lyons, H. R.: The Use of Radium in the Treatment of Myxomatous Nasal Polyps: Preliminary Report, Am. J. Roentgenol. **8**:407, 1922.

were observed in the fourteen cases treated with from 25 to 50 mg. of radium for two hours. He finds that radium will not cure the infection of the accessory nasal sinuses, which is the primary cause of the polyps; but, when used in conjunction with operative treatment, it prevents a recurrence of polyps.

NASOPHARYNGEAL FIBROMA

The nasopharyngeal fibroma is a tumor that occurs in boys between the age of 10 and 20 years. It is rarely seen in girls. This type of growth is mentioned in the writings of Hippocrates, who describe an operative method for its removal.

The tumor is benign in the sense that it does not metastasize; but, clinically, it is very different from the other benign tumors of the nasopharynx. It is composed of fibrous tissue with large cavernous blood spaces, especially prominent near the periphery. It grows by extension and invades the orbit, the accessory nasal sinuses, the pterygoid or temporal fossa, or the intracranial cavity. It is characteristic of this tumor that as it grows it becomes attached to the soft parts with which it comes in contact, and thus derives an additional blood supply. This characteristic renders surgical removal very hazardous; often a large fibroma is found to have many points of attachment, and the arteries that enter it may be as large as the external carotid. Mikulicz,[4] in 1899, gave the details of as many as twenty different methods of treatment, including the injection of chemicals, electrolysis, the use of snares and the various methods of surgical removal. The inaccessibility of the tumor and the difficulty in the control of hemorrhage are responsible for the high operative mortality and incomplete removal of the growth irrespective of the method employed.[5]

It is also characteristic of these tumors that they often cease to grow and gradually disappear after the age of 25, just as a fibroma of the uterus may disappear after the menopause. The growth originates from the fibrocartilage of the upper cervical vertebrae, basilar process of the occipital bone, or the internal lamina of the pterygoid process. Bensch,[6] in 1878, pointed out that these growths tend to disappear at the age when the sphenoid and the basilar processes of the occipital bones become united, and ossification of the cervical vertebrae is completed.

Histologically, a fibroma of the nasopharynx may be mistaken for a sarcoma. This is due to the fact that areas of embryonic connective

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4. Mikulicz, J.: Neubildungen des Rachen u. des Nasenrachenraumes, Handb. d. Laryngol. u. Rhinol. **2**:411-421, 1899.

5. Hellat, P.: Die sogenannten fibrösen Nasenrachenpolypen, Ort u. Art ihren Insertion u. ihre Behandlung, Arch. f. Laryngol. u. Rhinol. **25**:329-344, 1911.

6. Bensch, quoted by Ewing, Footnote 1.

tissue are always present, and, if only a small bit of the growth is excised, the microscopic appearance may be very misleading.

The most important clinical symptom is bleeding. One of our patients has had numerous spontaneous hemorrhages, with a loss of blood varying from 500 to 1,000 c.c. on each occasion. Removal of a small piece of growth for microscopic examination in one case was followed by such severe bleeding that transfusion was necessary.

Conservative treatment is particularly indicated in this type of growth. Although our experience has been limited to four cases, two

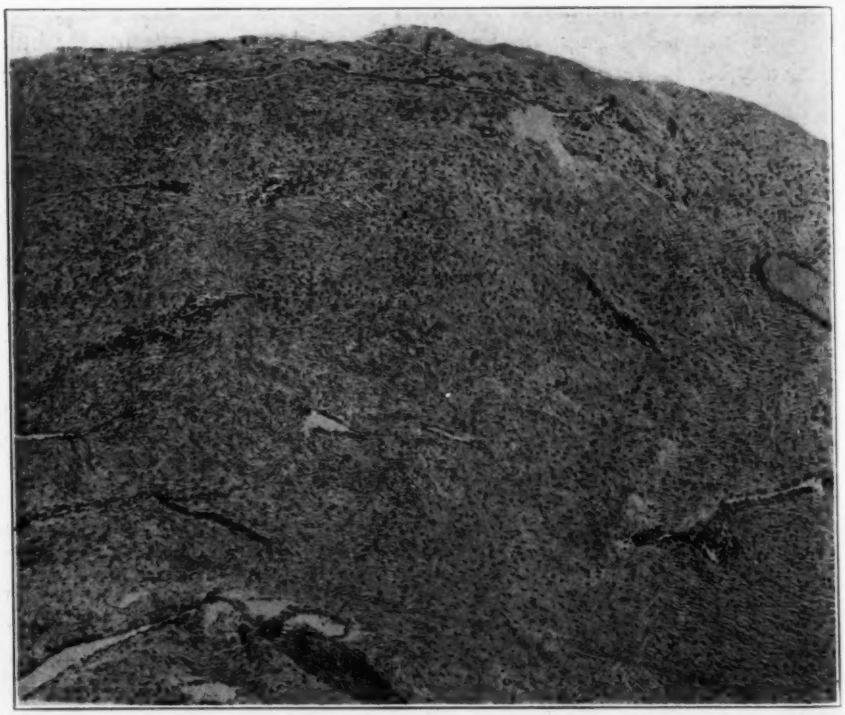

Fig. 1.—Fibroma of the nasopharynx in a youth, aged 20, treated by heavy irradiation followed by excision of the remainder of the growth; well three years later.

of these patients are well, and the other two are improving. The treatment has consisted of a combination of implantation of emanations, intranasal and external irradiation, and partial removal by operative methods. The details of the clinical history and treatment are given in Cases 1 to 4, inclusive. The microscopic appearance of a fibroma of the nasopharynx is shown in Figures 1 and 2. The growth in Figure 1 was cured with radium, while that shown in Figure 2 was cured by operation.

Fig. 2.—Fibroma of the nasopharynx in a man, aged 26, with a history of frequent hemorrhages, nasal obstruction and impaired hearing for four years; operative removal, no radium; well thirteen years later.

ANGIOMA

Angioma originating on the lateral wall of the nasal cavity is not such a rare condition as the textbooks would indicate. The very exhaustive articles by Heymann and Mikulicz in Heymann's Handbuch für Laryngologie only mention angioma in order to emphasize the infrequency of its occurrence in the nose and nasopharynx. The articles of Kümmel,[7] Marschik[8] and Oppikofer[9] do not mention this type of growth. The discussion of angioma of the nasal cavity in the textbooks of St. Clair Thomson, Wright and Smith and in the last edition of Denker and of Brünings is limited to the bleeding septal polyps and the varicosities of the septum that occur in Kiesselbach's area. We have had seven cases in which an angioma originated on the lateral wall in the posterior half of the nasal cavity and secondarily invaded the nasopharynx, and one case of a circumscribed submucous angioma, the size of a walnut, that originated and remained localized in the nasopharynx. The histologic appearance of the growth in six of these cases is that of a simple cavernous angioma, while in two cases, the microscopic appearance suggests an angiosarcoma. The clinical history and the absence of metastases to glands, involvement of cranial nerves, invasion of orbit or intracranial cavity justifies their classification as angioma. It should be emphasized again that the histologic appearance of a small fragment of nasal and nasopharyngeal growth does not justify an absolute diagnosis as to the nature of the growth or a final opinion as to the prognosis.

It is noteworthy that in this group of eight cases the first symptom of the growth appeared between the age of 16 and 28 years; the average age of onset was 20 years. The first symptom in every case was nasal obstruction.[10] In three cases tinnitus and impairment of

7. Kümmel, W.: Die Bösartigen Geschwülste der Nase, Handb. d. Laryngol. u. Rhinol. **3**:874, 1900.

8. Marschik, H.: Die Pathologie u. Diagnostik d. malignen Geschwülste der Nase und des Nasenrachenraumes mit Ausschluss der Nasenrachenfibrome, Beitr. z. Anat., Physiol. Path. u. Therap. d. Ohres [etc.] **7**:327-378, 1913-1914.

9. Oppikofer, E.: Ueber d. primären malignen Geschwülste d. Nasenrachenraumes, Arch. f. Laryngol. u. Rhinol. **27**:526-564, 1913.

10. The clinical history regarding nasal obstruction may be misleading in one respect. We have often seen a growth located in the posterior half of the nasal cavity on one side that pushed the septum over until it occluded the opposite side and caused bilateral nasal obstruction. We have seen this with benign growths—such as the fibroma and angioma, and in rapidly growing sarcomas. The carcinomas, on the other hand, rarely reach a size sufficient to push over the septum. They either ulcerate as rapidly as they grow or invade the septum and destroy it. Carcinoma involving the nasopharynx rarely reaches a size sufficient to give rise to obstruction to breathing as an early symptom.

hearing in one or both ears appeared at the same time, or soon after the nasal obstruction was noted. Pain across the bridge of the nose was present in one case; in the remaining seven, the growth caused no pain.

The duration of symptoms varied from two years to ten years before the patient came under our observation; the average was four years. In one case, a large cavernous angioma occupying the entire nasopharynx and obstructing both eustachian tubes had given rise to no symptoms until two weeks before admission, although the growth must have been present for several months.

Severe and frequent hemorrhages from the nose were a prominent feature in five of the eight cases in this group. It is of interest to note that four of the patients had had before admission one or more nasal operations in which a portion of the growth was removed. It is our impression that as a direct result of a partial removal the growth becomes infected and ulcerated, and thus endangers the patient's life from hemorrhage. For this reason, it is probably deleterious to the best interest of the patient to remove a piece of the growth for microscopic examination, and it is certainly not advisable to attempt the removal of the large nasal growths of this type through the nose. The fact that a piece of the growth had been removed was undoubtedly responsible for the frequent and severe hemorrhages in four of the five cases that presented this symptom.

There was unilateral exophthalmos in one case; but in none of the remaining seven cases was there any evidence of involvement of the orbit, intracranial cavity or any of the cranial nerves.

We have been unable to find any statistics of the complications or end-results of operative removal of large hemangiomas located in the posterior part of the nasal cavities or nasopharynx; but our experiences in one case (Case 6) convinced us that surgical extirpation of a growth of this character is an extremely hazardous procedure.

An abstract of the history of two of our cases with extensive nasal angioma will serve to illustrate the advantages and disadvantages of surgical treatment as compared with radium treatment:

CASE 6.—A white man, aged 33, was admitted to the Johns Hopkins Hospital in September, 1913, complaining of complete nasal obstruction and epileptic attacks. The first symptom, nasal obstruction, was noticed in 1903. Headache was first noticed during the latter part of 1912. He had his first general convulsive seizure in June, 1913, and, two months later, he had two similar attacks. These attacks were not focal and were not preceded by an aura.

An attempt was made to remove the growth through the nose in 1905. This operation was accompanied by such profuse bleeding that only a small fragment of growth was removed. The operation, however, was probably responsible for the fact that during the next eight years he had frequent and severe hemorrhages from the nose. During the two and one-half years follow-

ing the nasal operation, the patient said that he had received about 200 mg. hours of irradiation; but the amount of radium used or the method of application is not stated. This treatment was apparently of some value, for in 1908 his general condition began to improve and the nasal hemorrhages became less frequent.

In 1912-1913, however, the growth was evidently increasing in size, as evidenced by the obstruction to breathing, headaches and epileptic seizures. We, therefore, attempted to remove the growth by surgical operation. Under ether anesthesia, an approach was made through the left antrum. The control of hemorrhage was very difficult on account of the many large vessels that channeled the neighboring bony structures in the roof of the nose and entered the tumor at numerous points. It was impossible to clamp these vessels, and the use of bone wax was of little value on account of their size. After removal of the naso-antral wall and freeing the nasal portion of the growth, the operation was discontinued on account of the excessive bleeding. No attempt was made to remove the growth in the posterior part of the nasal cavity and the nasopharynx. It was necessary to pack the wound with gauze in order to control the bleeding. The infection of the accessory nasal sinuses and of the entire wound necessitated removal of the packs at frequent intervals, and during the five weeks following the operation there were numerous hemorrhages. The hemoglobin on the day of the operation was 92 per cent., and one month later had fallen to 29 per cent., with nucleated red cells in the circulation. The wound gradually closed, however, and, when the patient was discharged on the seventieth day after the operation, the blood count was 4,200,000 red cells, 6,200 white cells and 80 per cent. hemoglobin.

A letter from this patient in 1920, seven years after the operation, states that he has had no symptoms of epilepsy and no hemorrhages since leaving the hospital. The nasal obstruction gradually disappeared, and, for several years, he has been well.

It is not an uncommon experience in the surgical treatment of blood vessel tumors in any portion of the body to see the growth gradually regress and finally disappear after a partial extirpation. This is thought to be due to the fact that the portion removed is the primary point of origin or "nucleus" of the growth.

CASE 9.—A white boy, aged 18, was admitted to the Johns Hopkins Hospital in March, 1918, with a growth involving the left side of the nose and the entire nasopharynx, which had caused complete nasal obstruction for two years. There was some doubt from the histologic examination of the small piece of tumor removed from the nose as to whether the growth in this case was a simple cavernous angioma or an angiosarcoma. The important point is that this was an inoperable tumor on account of its location, size and vascularity, and that radium treatment has resulted in a disappearance of the tumor.

The first symptom of the growth in this case was difficulty in breathing through the left side of the nose. As the tumor increased in size, the nasopharynx became involved, and the nasal septum was pushed over until the right side of the nose became obstructed. Examination revealed that the growth had eroded the hard palate on the left and was appearing in the roof of the mouth. It is of interest in this connection to note that there is no history of pain. A piece of the growth was removed through the nose on two occasions, and each time the bleeding was profuse and difficult to control.

The general physical examination was negative, with the exception of a well compensated mitral lesion and a secondary anemia. There was no evidence of metastases to the glands of the neck, and the spleen was not enlarged. The blood Wassermann reaction was negative.

The radium treatment in this case consisted of external and intranasal irradiation and the implantation of one 4 millicurie emanation point in the nasopharyngeal portion of the growth. It is of interest to note that the growth decreased in size; the septum resumed its normal position, and, within a month after the first treatment, the patient was able to breathe through the right side of the nose for the first time in a year. Six months later, breathing was reestablished through both sides of the nose. The last examination, three and one-half years after the first radium treatment, disclosed no gross evidence of growth in the nose, nasopharynx or hard palate. The area in which the bone was destroyed in the hard palate healed without secondary infection.

SARCOMA

In selecting the material for this report, we have included only those cases in which the growth involved the nasopharynx. The cases with tumors limited to the nasal cavity or to the accessory nasal sinuses may be described in a subsequent publication. The primary point of origin is difficult to determine; but in eight of our twenty-six cases of sarcoma the history of involvement of the eustachian tube as one of the earliest symptoms suggests that the growth arose in the nasopharynx. In fourteen cases, however, nasal obstruction was an early symptom and suggests nasal origin. The statistics of Gurlt [11] indicate that sarcoma of the nasal cavity is four times as frequent as carcinoma. Mikulicz, in 1900, referred to the difficulty of recognizing the true nature of a nasal or nasopharyngeal growth by the histologic study of a small fragment, and suggested that many of the cases reported as sarcomas are probably very cellular or infected fibromas. Although metastasis to the cervical lymph glands may be the earliest symptom of a malignant growth in the nasopharynx it not infrequently happens that an ulcerated benign growth or a granuloma in this area is also associated with an early and pronounced enlargement of the neighboring glands. Marschik, in 1914, collected 853 cases of malignant tumor of the nose and of the accessory nasal sinuses. He finds that sarcoma is the most frequent type of malignant tumor in the nose, and that it tends to invade the sinuses secondarily; while the carcinoma arises most commonly within the sinuses and grows into the nose or the intracranial cavity. He also finds that the round cell sarcoma is frequent in the nasopharynx, but is rare in the nose or sinuses.

Marschik refers to the great variation in the histologic appearance of the nasopharyngeal fibroma, and to its similarity to sarcoma.

11. Gurlt, E.: Beiträge zur chirurgischen Statistik. I. Zur Statistik der Geschwülste, Arch. f. klin. Chir. **25**:421-467, 1880.

Mikulicz, in 1900, and more recently, Oppikofer directed attention to the fact that the microscopic diagnosis of a nasal or a nasopharyngeal tumor may be very misleading, and that every case must be thoroughly studied before a correct diagnosis can be made or an opinion ventured as to the outcome. Mikulicz cites as an illustration a patient with a granulation tissue tumor of the nose who was subjected to an extensive operation for sarcoma because the diagnosis was based solely on the inspection of the local condition and on the microscopic appearance of a fragment of the growth.

In the nose, especially, there is often an inflammatory zone around an early carcinoma that may cause confusion in the histologic recognition of the true condition. Oppikofer refers to the case of a man, 60 years of age, with a nasal tumor. The location, size and appearance of the growth, the age of the patient, and the symptoms all suggested a cancer; but it was necessary to remove three separate pieces before the clinical diagnosis was confirmed. The first piece removed resembled a fibroma with round-cell infiltration; the second piece was diagnosed as a round-cell sarcoma; the third piece, removed from a point near the attachment of the tumor, showed an adenocarcinoma.

Two mistakes are so frequently made by nose and throat specialists that they deserve special mention:

1. The mistake is made of removing a small piece of a nasal or nasopharyngeal tumor and accepting the microscopic report of the pathologist as the true diagnosis of the clinical condition, without taking into consideration the clinical data and the results of statistical studies regarding the age and sex incidence of the various types of new growths in the nose. For example, a vascular, cellular fibroma is the common tumor of the nasopharynx in males from 10 to 20 years of age. It is rare in females at any age. The lymphosarcoma, in adults, is a common tumor of the nasopharynx but rarely occurs as a primary growth in the nose. The spindle-cell and the fibrosarcoma are the most common of the malignant tumors arising in the nose. According to the statistics of J. A. Watson,[12] Klein,[13] Sonnenschein[14] and Oppikofer,[9] sarcoma of the nasal cavity and of the nasopharynx is almost as frequent after the age of 40 as it is in younger persons. A sarcoma usually forms a larger tumor in the nose than does a carcinoma. This is due

12. Watson, J. A.: Sarcoma of the Nasal Passages: An Inductive Study Based on the Records of 150 Cases, Am. Med. **7**:553-556, 1904.

13. Klein, H.: Pathologisch-histologische Studie über eine seltene Combination von Sarkom und Carcinom der Nasenhöhle, Würzburg, A. Boegler, 1898, p. 33.

14. Sonnenschein, R.: Ein langdauernder Fall von Sarcoma nasi, Arch. f. Laryngol. u. Rhinol. **22**:528-539, 1909.

to the fact that carcinomas ulcerate at an early stage. Obstruction to nasal respiration and ear trouble, due to involvement of the eustachian tube, are the earliest symptoms of sarcoma; while pain, due to involvement of some branch of the trigeminus, difficulty in opening the mouth, enlarged glands of the neck and bleeding are early symptoms of carcinoma. Glandular metastases appear late in nasal tumors. A sarcoma of the nose or antrum may persist for months or even years and reach an enormous size without involvement of the cervical lymph glands, while the first evidence of a carcinoma or of a lymphosarcoma of the nasopharynx is often the rapid and painless increase in size of the deep cervical glands at the angles of the jaw. Only fourteen of our twenty-six cases of sarcoma of the nasopharynx have palpably enlarged glands of the neck, while in thirteen of our sixteen cases of carcinoma, metastasis to the neck is a prominent finding. One of our carcinoma patients had an extensive operation on the glands of the neck on two occasions, although the severe pain and the location of the glands should have suggested that the primary growth was in the nasopharynx. In another case, blood stained discharge from the nose and mouth and a tremendous enlargement of the cervical glands were the only symptoms of a primary carcinoma of the nasopharynx. The size of the glands may be noted in Figure 19. The primary growth in this case never reached a size sufficient to cause nasal obstruction or a change in the character of the voice. It is of interest to note that this patient received tuberculin treatment for several months on the assumption that the glands were tuberculous. The true nature of the malady was only recognized when an examination of the nasopharynx revealed a small ulcerated growth, and a gland was removed from the neck for microscopic diagnosis. New [15] has recently published, from the Mayo Clinic, two important papers on the symptoms of nasopharyngeal tumors and the mistakes that are made in the early diagnosis of tumors arising in this area. He reports seventy-nine cases; thirty-four were epitheliomas and thirty-three lymphosarcomas. The symptoms were referable to the eye in twenty-one; to the ear in twenty-nine; to the nose and pharynx in thirty-eight; to the glands of neck in fifty-one; to the gasserian ganglion in four; to the jugular foramen in two, and to the intracranial cavity in eleven cases. It is especially instructive to note that, of these seventy-nine patients, seventy-four had had an operation for the relief of symptoms without recognition of the fact that a primary growth in the nasopharynx was the cause of these symptoms. In twenty-four

15. New, G. B.: Syndrome of Malignant Tumors of the Nasopharynx, J. A. M. A. **79**:10-14 (July 1) 1922; The Relation of Nasopharyngeal Malignancy to Other Diagnosis, Minnesota Med. **4**:419-422 (July) 1921.

patients, the tonsils and adenoids had been removed; in eighteen, the glands of the neck; in twelve, the third molars had been extracted; various intranasal operations had been performed in nineteen, and a mastoid operation had been performed for the relief of pain that was due to the growth and not to infection, in one case.

2. The second mistake is that of removing a tumor of any kind from the nose or nasopharynx and discarding the tissue without a gross or microscopic examination. One of our patients, a woman, aged 33, was admitted in October, 1915, with a history of nasal obstruction for four years. "Polypi" had been removed from the nose every two or three months from 1912 to 1915. During the early part of 1915, the operations were necessary every month, and later every week. The tissue removed at the various nasal operations was not saved, and no microscopic examination had ever been made prior to her admission here in October, 1915. The growth proved to be a very cellular angiosarcoma, and death resulted from intracranial invasion. We have had two other patients in whom a lymphosarcoma was not recognized for several months after the appearance of clinical symptoms because the tissue removed from the nasopharynx was discarded without examination.

The result of radium treatment in the various types of sarcoma is given in Cases 5 to 33, inclusive. The point we wish to emphasize now is that every growth removed from the nose and throat should be investigated, grossly and microscopically; but, on the other hand, the diagnosis of such growths should not be based on the microscopic appearance of a small fragment, without taking into consideration all of the clinical and laboratory data that are available.

It is doubtful, indeed, whether the removal of a piece of a tumor for diagnosis is ever a justifiable procedure. We have removed tissue for a microscopic diagnosis in nearly every case included in this report, because we wished to study the reaction of the various types of new growth to radium. It is possible, however, that incomplete operative removal or even the removal of a small fragment, either before or during the irradiation, is responsible for the reappearance of the growth in some distant part of the body. If the growth is a very vascular sarcoma or a true angioma, the deleterious effect of a partial removal is apparent in the increased frequency and severity of the hemorrhages. In the majority of our cases of sarcoma, angioma and fibroma bleeding was not a prominent symptom until a portion of the growth had been removed. After the nasal operation, however, the growth becomes infected, and hemorrhages are severe and frequent. We have seen patients with a benign angioma in the nose who had all of the clinical symptoms of an advanced malignant growth. The history of these

patients is that they have noticed difficulty in breathing through the nose or a feeling of fulness in the ear. They consult a physician who discovers the growth and attempts its removal. After this hemorrhages are frequent. The tumor becomes infected; the nose is filled with a purulent discharge containing saprophytic spirochetes and organisms of all kinds; the glands of the neck become enlarged, and the cachectic condition of the patient is due to the loss of blood, to the local infection and to the digestive disturbances that are secondary to the long continued swallowing of the purulent discharge.

In our series of twenty-seven cases of sarcoma in which the nasopharynx was involved, the tumors are classified as follows: lymphosarcoma, 10 cases; spindle cell sarcoma, 2 cases; myxosarcoma, 3 cases; angiosarcoma, 5 cases; round-cell sarcoma, 3 cases; alveolar sarcoma, 1 case; fibrosarcoma, 1 case; osteosarcoma, 1 case, and no microscopic diagnosis, 1 case.

LYMPHOSARCOMA

The earliest symptoms in the ten cases that we have included in the lymphosarcoma group were: (1) disturbance of hearing in four cases due to obstruction of the eustachian tube; (2) difficulty in breathing through the nose in two cases; (3) enlarged glands of the neck in four cases; (4) sore throat for four months in one case. Pain due to involvement of the trigeminus was present in two cases, the second division in one, the second and third divisions in the other. It is worthy of note that, in two cases, the growth appeared within three weeks after the operative removal of the tonsils and adenoids. One of these patients, a girl, aged 2½ years, had a history of frequent colds and of having been a "mouth breather" since infancy. A swelling was noticed in the soft palate and the lateral wall of the pharynx two weeks after the operation. We saw this patient for the first time about a month after the tonsillectomy, and the microscopic appearance of the growth is shown in Figure 8. In the second case, a girl, aged 10½ years, the tonsils and adenoids had been removed because of pain and swelling of the left knee and of the right shoulder, although there was no history of an infection of the upper respiratory tract. The rapid enlargement of the glands at the angle of the jaw on the left was the first indication of the growth. When we first saw this child, four weeks after the tonsillectomy, the soft palate and lateral wall of the pharynx on the left were involved. There were no normal landmarks in the nasopharynx. It is unfortunate that in both of these cases the tonsils and adenoids removed at operation were not saved for microscopic examination.

Detailed data concerning the treatment and results in each of these ten cases are given in the reports of Cases 15 to 24, inclusive.

ANGIOSARCOMA

The next largest group, angiosarcoma, consists of five cases. The orbit was invaded by the growth in two patients in this group; but these two and a case of lymphosarcoma are the only instances in our entire series of twenty-seven cases of sarcoma in which this complication was present. Frequent and severe nasal hemorrhages were a prominent symptom in three cases. One of these patients, however, had two nasal operations, and the bleeding was possibly due to secondary infection of the tumor. Unilateral nasal obstruction was the earliest symptom in three cases and suggests that the growth originated in the nose and involved the nasopharynx secondarily. Only one of the patients in this group had metastases in the glands of the neck. The eustachian tube was involved in one case.

A detailed report of the symptoms, method of treatment and result in the cases classified as angioma and angiosarcoma is given in the reports of Cases 5 to 14, inclusive.

MYXOSARCOMA

The myxosarcoma group includes three cases. We have classified these tumors as myxosarcoma because they are clinically malignant, and, although very cellular, the individual cells are widely separated by loose poorly staining interstitial material. Photomicrographs of two of these cases are shown in Figures 10, 11 and 12. Nasal obstruction as an early symptom was present in each of these cases, and suggests that the growth arose in the nose. In one case, the growth involved the antrum and later broke through the hard palate. There were no metastatic glands in the neck, no involvement of the orbit or cranial cavity and no history of bleeding in any of these three cases.

The growth was removed by surgical operation in one case; but the patient died within twenty-four hours with symptoms of shock. The two remaining cases were treated with radium alone:

CASE 27.—A boy, aged 16 years, reported that the first symptom was nasal obstruction on the left, one and one-half years before admission. The onset of this symptom followed a severe coryza. The child had never had an illness of any kind, with the exception of measles and whooping cough. On admission, the posterior half of the left nostril and the entire nasopharynx were filled with growth. The nasal septum was pushed to the right, thus occluding the right nostril. The growth had not perforated the septum. From the examination, it seemed probable that the growth had originated in the left middle turbinate or in the mucous membrane just below it.

The radium treatment, consisting of 83,000 millicurie hours of gamma radiation, was applied externally to both sides of the head at a distance of from 2 to 5 inches; 1,800 millicurie hours of gamma radiation was applied directly to the surface of the growth, and two capillary glass tubes, each containing 5

millicuries of radium emanation, were implanted into the growth in the nasopharynx. This treatment caused a burn that resulted in a perforation of the soft palate, but caused no apparent injury to the brain, hypophysis or the eustachian tubes. There was very little, if any, decrease in the size of the growth during the first year of radium treatment. After this, the tumor began to ulcerate, and two years later had entirely disappeared from the nasal passages and from the nasopharynx. The patient was in good health in 1921 and weighed 126 pounds (57 kg.).

In the remaining case (Case 29) there was an extensive growth that, on admission, involved the antrum and the hard palate. The growth was apparently not affected by the three heavy internal irradiations of 46,500 millicurie hours at a distance of from 5 to 6 inches (12.5 to 13 cm.) that he received during a period of ten weeks. Soon afterward, the growth appeared under the malar arch, and the treatment was discontinued. This patient is dead.

Our experience has shown that myxomatous tissue is very resistant to radium. The benign myxomatous polyp that often appears in the nose in association with a pyogenic infection of the accessory nasal sinuses will not disappear after the surface application of beta or gamma irradiation. We have not implanted capsules of emanation into benign polyps. We mentioned above the experiences of the Mayo Clinic in the treatment of myxomatous nasal polyps with radium. Lyons [3] concludes that radium treatment may stimulate the production of fibrous tissue and thus transform a myxomatous polyp into a fibromyxoma. The more fibrous tissue a polyp contains the less tendency it has to recur after surgical removal. Until we know more concerning the effects of irradiation on the surrounding tissues, such as the retina, vessels of the orbit, optic nerve and base of the brain, it does not seem justifiable to employ radium in anything but the inoperable tumors in this region.

The data in regard to the other types of sarcoma in our series—the duration of the growth, the clinical symptoms and the result of treatment—are given in Cases 25 to 33, inclusive. In our experience, the spindle-cell, round-cell and myxomatous sarcomas are less favorable for radium treatment than are the more vascular types.

CANCER

We include in this group sixteen cases that have been observed during the last twelve years. The diagnosis of cancer was confirmed in every case by the histologic examination of a fragment of the growth. Every patient in this group is dead: Six had definite evidence of intracranial invasion; ten had frequent and severe hemorrhages from the mouth or nose, or a history of a bloody discharge; thirteen had metastases to the glands of the neck, and, in nine instances, there was

such a marked fixation of the jaw that the patients were unable to take solid food. These are the outstanding clinical symptoms in carcinoma of the nasopharynx, and they differ markedly from the symptoms caused by the sarcomas or any of the benign tumors that involve this region. These symptoms of cancer, however, are the late manifestations of the growth, and, when they are all present, the condition is too far advanced for a cure by any method.

We have carefully gone over the history of each of these sixteen patients in order to tabulate the earliest symptoms of carcinoma of the nasopharynx:

1. It is noteworthy that in two patients a constant discomfort and soreness of the throat were the first symptoms. It is difficult to secure accurate data as to how long the sore throat had been present before the other evidences of a new growth became evident; but certainly an early carcinoma should be considered in the differential diagnosis of the cause of a slight soreness in the nasopharynx and pharynx that persists for several weeks. The other common causes of a persistent sore throat are: (1) the secondary and tertiary lesions of syphilis; (2) the tuberculous ulcerations of the pharynx secondary to a pulmonary infection, or (3) the primary tuberculous lesions of the lymphoid tissue in the tonsils or the nasopharynx that do not ulcerate and that can but rarely be recognized until the tissue is removed for microscopic examination or the glands of the neck become involved; (4) infection with Vincent's organisms, and (5) a chronic pyogenic infection of the tonsils and adenoids.

2. In seven patients, the first symptom of the carcinoma in the nasopharynx was impairment of hearing, a feeling of fulness, and later pain and discharge from one ear. These symptoms are due to the fact that the growth originates near the pharyngeal orifice of one of the eustachian tubes. In three of these seven cases, the patient first consulted an otologist on account of a feeling of fulness in one ear or impairment of hearing. In each case, the symptoms were treated from two to seven months, and the primary condition in the nasopharynx was not recognized until the involvement of adjacent nerves, muscles or glands made the diagnosis evident. The failure to recognize these nasopharyngeal growths at an early stage is due to careless and inefficient methods of examination. A reflex cough and an irritable pharynx are often early symptoms of a growth in the posterior part of the nose or nasopharynx, whether the tumor is due to a benign hypertrophy of the posterior end of the turbinates or is malignant. This irritability of the pharynx makes it difficult to use a pharyngeal mirror, and many laryngologists and otologists are either too busy or too impatient to anesthetize the pharynx with cocain or to inspect the nasopharynx with

an electrically lighted nasopharyngoscope. There is little prospect of ever curing a carcinoma of the nasopharynx with either radium or operation if the growth is not recognized before the adjacent tissues have been invaded.

3. Recognizable metastases to the glands appear late in nasal tumors, while in primary nasopharyngeal growths enlarged glands near the angles of the jaw appear early. In one of the patients in this series, the glands of the neck had been removed on two occasions before the primary growth in the nasopharynx had reached a size sufficient to direct attention to this region. In another patient (Fig. 19), the enlarged glands were for several months regarded as evidence of tuberculosis or Hodgkin's disease, and their true nature was not suspected until tissue was excised for diagnosis. The slight but persistent sore throat and the occasional bleeding in this case were, for the period of a year, the only symptoms of the primary nasopharyngeal growth. In a third case, the only symptom for a period of three months was an enlarged gland near the angle of the jaw on the left, and the first indication of a nasopharyngeal lesion was a gradually developing stiffness of the jaw and inability to open the mouth. A possible explanation of the rapid enlargement of the metastatic glands in the neck, while the primary nasopharyngeal cancer does not become large enough to cause obstruction to breathing, is the tendency of the carcinomas of the mucous membrane in this region to ulcerate as rapidly as they grow. The sarcomas of the nasopharynx, on the other hand, usually grow rapidly, do not ulcerate unless injured and cause obstruction to breathing at an early stage.

Dr. G. B. New,[16] in a recent review of forty-six cases of malignant tumor of the nasopharynx observed at the Mayo Clinic, found that in twenty-two of the forty-six cases there were no symptoms referable to the nose or throat. On account of the variability of the symptoms, some of the patients had been subjected to various operations and treatments, such as the extraction of teeth, treatment for syphilis, removal of the glands of the neck, paracentesis, intranasal operations, tonsillectomy and operation for pituitary tumor. The failure to recognize the primary growth in the nasopharynx was due to the fact that this region was never examined.

In Cases 34 to 49, inclusive, the symptoms and the objective findings in each of our sixteen cases of carcinoma of the nasopharynx are recorded. Many of these symptoms, however, are the late manifestations of the growth, and, when they are present, there is little hope of effecting a cure with any methods of treatment.

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16. New, G. B.: Footnote 16, second reference.

COMMENT

There is an extensive literature on the subject of nasal and nasopharyngeal growths,[17] but very little has been written in regard to their treatment with radium. In this paper we have said but little about the detailed technic of irradiation. Radium as a therapeutic agent is more dangerous than the roentgen ray, and should be employed only by those who, in addition to their medical education, are thoroughly familiar with physics and higher mathematics. A large clinical experience and a careful correlation of dosage, method of application and result, in the various types of new growths, are essential for the training of a radiologist. For example, it is conceivable that a physician or surgeon, untrained in biophysics, might advise a patient with a localized lymphosarcoma in the throat to have prophylactic irradiation of the mediastinum, abdomen and the glands in the axilla and groin, but a physicist would recognize immediately that such a plan of treatment would result in profound changes in the blood and probably hasten the death of the patient.

Radium treatments in all of our cases have been planned and executed by Dr. Curtis F. Burnam of the Howard A. Kelly Hospital in Baltimore. The amount of radium used and the method of application in our cases are given in the tables, but we do not feel competent to discuss the details of these treatments.

We have mentioned above the difficulties of classifying these nasal and nasopharyngeal tumors by the microscopic examination of a small fragment of the growth. It is sometimes impossible to differentiate a sarcoma from a carcinoma; an angioma from an angiosarcoma; or a cellular fibroma from a sarcoma. For this reason, we have reported our cases at length, giving the age, sex, duration of symptoms, clinical findings, treatment and end-result. The diagnosis of the type of tumor may be incorrect in several instances; but we have attempted to present these cases from a biologic point of view, and believe that the accumulation of sufficient data of this kind will be a great aid to the clinician.

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17. The most instructive articles are those of Heymann, Kümmel and Mikulicz in Heymann's Handbuch für Laryngologie; Harmer and Glas (Die malignen Tumoren der inneren Nase [Eine klinische histologische Studie], Deutsch. Ztschr. f. Chir. **79**:433-539, 1907); Marschik; Oppikofer; Berthold Müller (Zur Pathogenese und Therapie der Nasenrachenfibrome, Ztschr. f. Ohrenh. **70**:145-179, 1914); Pollak (Ueber die "endothelialen" Geschwülste der Nase und ihrer Nebenhöhlen, Arch. f. Laryngol. u. Rhinol. **25**:383-400, 1911); J. A. Watson; G. B. New, and Schmiegelow (Einige Beobachtungen hinsichtlich der Wirkung des Radiums auf inoperable maligne Neubildungen im Munde, Rachen und in der Nase, Arch. f. Laryngol. u. Rhinol. **33**:1-18, 1920).

One outstanding result of the radium treatment of these cases is the high percentage of cures in the vascular tumors. In such an inaccessible region as the nasopharynx, the large vascular tumors are not suitable for surgical removal; but if untreated, they not only become infected, ulcerate and bleed profusely, but may destroy the neighboring structures by pressure, and grow into the orbit and intracranial cavity. Clinically, this type of tumor, although it may not metastasize, is as serious in its consequences as a malignant growth. Although these vascular tumors do not disappear so rapidly after irradiation as do some other types, for example, lymphosarcoma, the end-result is much better. A large lymphosarcoma with metastatic glands in the neck may disappear entirely within a few weeks after the first radium treatment, while a hemangioma of the same size may require four or five years to effect a cure. We have at least two patients who had myxosarcoma involving the nose and nasopharynx that are well. The microscopic appearance of this tumor is shown in Figure 10, and, by referring to Cases 27 and 33, it will be seen that tremendous irradiation, extending over a period of several years, has been necessary to effect a cure.

No case of carcinoma of the nasopharynx in this series has been cured; but, in many cases, the symptoms have been ameliorated. In some instances, the rapid decrease in size of the primary growth leads us to believe that the unfavorable outcome is due to the fact that these patients do not apply for treatment until metastases have occurred.

It is important for the medical profession to know that tumors in the posterior part of the nose and in the nasopharynx are not uncommon, and that their earliest symptoms may be referable to the ear, the eye, the glands of the neck or to the area of distribution of some branch of the trigeminal nerve. The recent publication of New from the Mayo Clinic is very instructive. During the last six years, he has observed seventy-nine patients with a malignant growth in the nasopharynx, and he states that seventy-four of these patients had had an operation of some kind for the relief of symptoms without recognition of the primary growth in the nasopharynx.

REPORT OF CASES

FIBROMA OF THE NASOPHARYNX

CASE 1.—*History.*—A white boy, aged 15, was admitted in March, 1920, complaining of inability to breathe through the nose, the onset of which had occurred four years previously. Several pieces of growth had been removed by his home physician, three years previously; but none of this tissue was available for microscopic examination. Frequent and severe hemorrhages had occurred during the previous three years. A swelling had been present on the right side of the face for two years, also tinnitus in the right ear.

Examination.—The Wassermann reaction was negative. No metastatic glands were discovered in the neck. The growth, which had originated in the nasopharynx, had grown into the right nostril, ethmoidal sinuses and antrum, causing swelling on the right side of the face. There had been no loss in weight. The growth in the nasopharynx was smooth and soft. The hard palate protruded into the mouth.

Diagnosis.—No tissue was removed on account of the history of severe hemorrhages. The clinical diagnosis was fibroma.

Treatment.—Intensive irradiation was used, March 4 and Sept. 3, 1920, a total of 42,600 mc. hours of gamma radiation at a distance of 5 inches being employed over the right side of the face. Eleven millicuries of radium emanation was implanted in the growth in glass capillary tubes.

Course.—September, 1920, the growth had increased in size, filling the nasopharynx and the right side of the nose. The septum was pushed over to the left, thus occluding the left nostril. The growth was sloughing at the site of implantation of the radium. The glands of the neck were not enlarged.

Case 2.—*History.*—A white boy, aged 16, was admitted in October, 1919, complaining of inability to breathe through the nose and bleeding. The adenoids had been removed a year previously, but none of this tissue was available for microscopic examination. Frequent and severe hemorrhages had occurred during the past year. A growth, which had been discovered in both sides of the nose, ten months previously, had been partially removed, followed by a severe hemorrhage. This impaired the hearing in both ears; but the impairment was worse in the left.

Examination.—The Wassermann reaction was negative. No metastatic glands were discovered in the neck. There was no pain. There was a bloody discharge from the nose. A huge growth was found in the nasopharynx pushing the soft palate forward, causing difficulty in breathing through the mouth at night and complete nasal obstruction. The orbit, intracranial cavity and antrums were not involved.

Diagnosis.—No tissue was removed on account of the history of a severe hemorrhage. The clinical diagnosis was fibroma.

Treatment.—Between Oct. 25, 1919, and June 23, 1920, the patient received intensive radium treatment from the outside, directly against the tumor in the nasopharynx and by implantation, a total of 40,900 mc. hours of gamma radiation was applied over the outside, at a distance of 4 inches. Seven hundred and fifty millicurie hours of gamma radiation was employed against the tumor in the nasopharynx, and 23½ mc. of radium emanation, in glass capillary tubes, containing from 1 to 3 mc. each, was implanted into the tumor.

Course.—November, 1919, there was considerable irritation due to the radium and severe pain. The growth had decreased in size.

December, 1919, the growth was invisible in the mouth; but the nose and nasopharynx were still filled with the growth.

January, 1920, there had been no decrease in the size of the growth during the previous month.

June, 1920, the growth had become smaller, allowing a little breathing through both sides of the nose. The hearing was normal. There were no headaches, no pain or fixation of the jaw. There were no enlarged glands in the neck. A very severe hemorrhage occurred a few days previously.

CASE 3.—*History.*—A white boy, aged 18, was admitted in June, 1915, complaining of nasal obstruction, but with no headache or bleeding.

Examination.—The Wassermann reaction was negative. A large, soft, pink mass had originated in the left side of the nasopharynx and had grown into the nose posteriorly on the left. There were no eye or ear symptoms, and the glands in the neck were not enlarged.

Diagnosis.—The clinical diagnosis was fibroma.

Treatment.—Between June 25, 1915, and June 29, 1916, the patient was given five rather intense intranasal irradiation treatments and heavy treatment from the outside, with a total of 1,250 mc. hours of gamma radiation. An external irradiation, consisting of 1,000 mc. hours, was employed at a distance of 2 inches, over the left side of the face.

Course.—December, 1915, the growth was much smaller. Breathing was well established in both sides of the nose. There was still a small growth in the nasopharynx and in the posterior half of the nose on the left. There was no bleeding or ulceration.

June, 1916, there was still a small growth, but breathing was good. There were no subjective symptoms.

March, 1917, the growth had entirely disappeared, and the general health was excellent.

CASE 4.—*History.*—A white man, aged 20, was admitted in January, 1918, complaining of nasal obstruction, with bleeding from the nose and the mouth. The adenoids were removed in April, 1917, but no microscopic examination had been made of this tissue. A growth had been discovered in the left side of the nose and nasopharynx, two months later. A piece was removed and diagnosed as sarcoma.

Examination.—The Wassermann reaction was negative. No metastatic glands were found in the neck. There were no ear symptoms and no headache. The differential blood count was normal. The growth occupied the left side of the nasopharynx and the anterior wall of the sphenoidal sinus on the left.

Diagnosis.—The clinical diagnosis was fibroma.

Treatment.—The report of the radium treatment was lost from the history; but the amount of irradiation was approximately the same as in Case 3. A portion of the growth in this case was removed, and, on one occasion, 542 mc. of radium was applied directly in the wound for eleven minutes.

Course.—May, 1918, there had been no bleeding since the first radium treatment. The patient had gained 20 pounds during the previous three months. There was a crater-like depression in the region formerly occupied by the growth. The area was now covered with a normal appearing mucous membrane.

December, 1918, the patient was well, and there was no recurrence.

June, 1921, the patient was well and there was no recurrence.

ANGIOMA AND ANGIOSARCOMA OF THE NASOPHARYNX

CASE 5.—*History.*—A white woman, aged 28, was admitted in May, 1913, complaining of tinnitus, with an impairment of hearing on both sides, of two weeks' duration.

Examination.—The Wassermann reaction was negative. There had been no history of bleeding. There were no enlarged glands of the neck. A large, firm growth occupied the entire nasopharynx, obscuring both eustachian tubes, with a middle ear type of deafness.

Diagnosis.—The clinical diagnosis was hemangioma (Fig. 3).

Treatment. — The patient received no radium treatment. The growth was removed after splitting the soft palate. About 0.5 cm. of the right eustachian orifice was removed with the growth, with no subsequent dilatation of the tube. There was very little bleeding during the operation, and no postoperative bleeding.

Course.—February, 1921 (nearly eight years after the operation), the patient was perfectly well, and there was no evidence of any recurrence. The voice was normal. The hearing, also, was normal on both sides. The orifices of both eustachian tubes were open, and the orifice of the right tube was of about normal size.

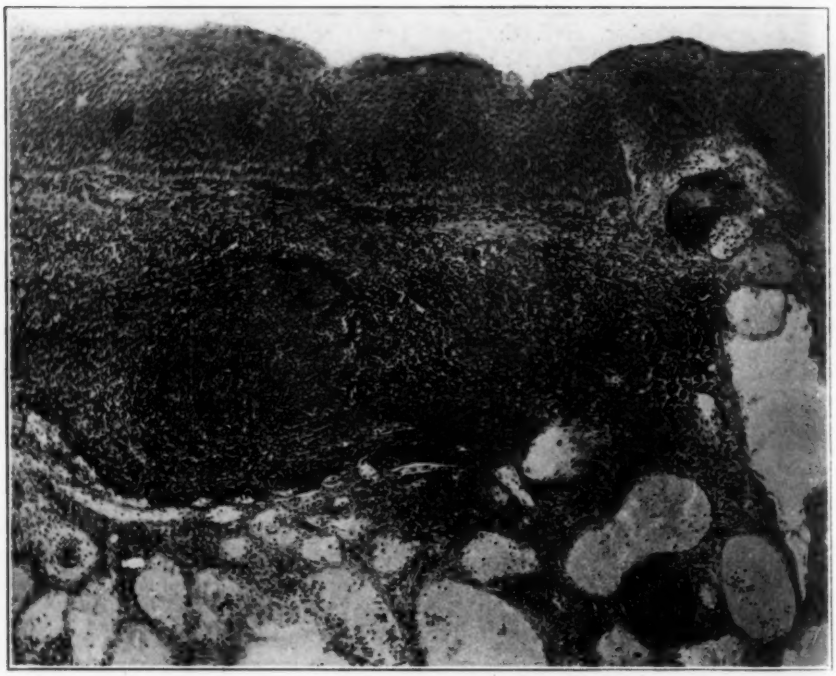

Fig. 3.—Angioma originating under mucous membrane of nasopharynx in a woman, aged 28; no history of bleeding; operative removal, no radium; well eight years later.

CASE 6.—*History.*—A white man, aged 33, was admitted in September, 1913, complaining of a nasal obstruction of ten years' duration, epilepsy of four years' duration and frequent and severe nasal hemorrhages. The patient had had numerous nasal operations during the last nine years, which were always followed by severe hemorrhages.

Examination.—The Wassermann reaction was negative. There were no enlarged glands of the neck and no ear symptoms. A growth arose from the lateral wall of the right nostril, filling the nasopharynx, and was adherent to the septum posteriorly. The neurologic examination was negative. Dr. H. M. Thomas believed that the patient was suffering from epilepsy.

Diagnosis.—The clinical diagnosis was hemangioma (Fig. 5).

Treatment.—No radium treatment was employed. The patient said that he had received 200 mg. hours before admission, which for a time improved his

Fig. 4.—Angioma occupying the left side of the nose and entire nasopharynx in a man, aged 25, showing the large ulcerated area in contrast to Figure 3. Bleeding was a prominent symptom; radium treatment; patient well four years later.

condition. The growth was removed by operation. An incision was made over the right antrum; but the antrum was not involved. The entire lateral wall of the nose, the mucous membrane of the floor of the nose and the posterior half of the septum were all removed in one piece. The profuse hemorrhage at

operation was controlled by packing. At one time, blood examination revealed: erythrocytes, 2,000,000; leukocytes, 6,500; hemoglobin, 29 per cent. Many of the erythrocytes were nucleated. The blood pressure was 72. Blood transfusion was not performed.

Course.—January, 1921 (nearly eight years after operation): The patient has been perfectly well since leaving the hospital. There has been no recurrence of bleeding, and he breathes normally through both sides of the nose. He has not had an epileptic attack since leaving the hospital.

Fig. 5.—Angioma involving entire right nostril and nasopharynx in a man, aged 33; history of frequent hemorrhages and epileptic attacks for four years; operative removal; no radium; severe postoperative hemorrhages, hemoglobin rose to 29 per cent.; well eight years later; no epileptic attacks since operation.

CASE 7.—*History.*—A white man, aged 25, was admitted in February, 1917, complaining of a nasal obstruction on the left side, with frequent hemorrhages from the mouth and the nose, of about four years' duration. There had been no headaches and no ear symptoms.

Examination.—The Wassermann reaction was negative. A growth filled the posterior half of the left nostril and the entire nasopharynx. There were no enlarged glands in the neck. There was a history of nasal operation, three years previously, which was followed by a severe hemorrhage and a rapid

recurrence of the growth. A piece of the growth was removed for microscopic examination, and severe bleeding followed. A roentgen-ray examination of the chest revealed nothing abnormal.

Diagnosis.—The clinical diagnosis was hemangioma (Fig. 4).

Treatment.—Between Feb. 27, 1917, and April 16, 1917, the patient had received heavy external irradiations and a mild irradiation in the posterior pharynx. The external treatment consisted of 60,800 mc. hours of gamma radiation, being employed at a distance of 3 inches, and distributed over both sides of the face and both sides of the nose. The intranasopharyngeal treatment consisted of 250 mc. hours of gamma radiation employed directly against the growth in the nasopharynx. In this case, also, the hemorrhages from the nose and the mouth stopped after the first irradiation, and never recurred.

Course.—March, 1917, the patient had markedly improved and could breathe much better. There had been no recent bleeding.

April, the growth had entirely disappeared from the left side of the nose; but there was still a considerable mass of tumor in the nasopharynx.

February, 1921, the patient had free breathing space on both sides and had been working regularly since June, 1917. No bleeding recurred, and there was no evidence of the growth in the nose or nasopharynx.

CASE 8.—*History.*—A white youth, aged 19, was admitted in January, 1917, complaining of a nasal obstruction on the right, of three months' duration, with severe bleeding from the nose and mouth. He had no headache and no ear symptoms.

Examination.—The Wassermann reaction was negative. A growth filled the nasopharynx and the posterior part of the nose on the right, pushing the septum over and causing a partial obstruction on the left. There was no evidence of metastases in the neck. The neurologic examination was negative.

Diagnosis.—The clinical diagnosis was angiosarcoma.

Treatment.—Between Jan. 26, 1917, and Feb. 18, 1919, the patient had received intensive irradiation, a total of 77,200 mc. hours of gamma radiation being employed at a distance of from 3 to 4 inches, centered over the right side of the face. He had also received 600 mc. hours of gamma radiation applied directly against the growth in the posterior nares. The cessation of the nasal hemorrhages was very striking in this case. Jan. 24, 1917, the hemoglobin was 58 per cent.; one month later, it was 78 per cent. During this period, irradiation was the only treatment that the patient received.

Course.—January, 1917, persistent and severe nausea occurred after the irradiation.

April, 1917, the patient was able to breathe through both sides of the nose; but the growth was still visible in the nose and the nasopharynx. The weight was 140 pounds, which was a gain of 6 pounds during the past month. The general health was excellent.

November, 1918, there was a marked improvement. A small amount of the growth was still attached to the posterior part of the septum, as well as between the posterior end of the middle and inferior turbinate on the right. Both of the eustachian tubes were clear for the first time. There was still a little growth in the left fossa of Rosenmueller.

February, 1919, there was no evidence of metastases; but there remained a small piece of growth in the posterior end of the inferior turbinate region on the right.

January, 1922, the patient wrote that he was in the best of health.

CASE 9.—*History.*—A white boy, aged 18, was admitted in March, 1918, complaining of a chronic nasal discharge since infancy. There was a history of a nasal operation, eighteen months previously, which was followed by a severe hemorrhage. The entire nasopharynx was filled with a growth which pushed the septum over, causing a complete nasal obstruction on the left.

Examination.—The Wassermann reaction was negative. The growth apparently had originated in the left side of the nose, and involved the entire nasopharynx. It had eroded through the hard palate on the left, but not through the mucous membrane. No metastatic glands were found. Bleeding had been a prominent symptom. Aside from a secondary anemia, the general physical examination was negative. There was no history of headache or pain.

Diagnosis.—The clinical diagnosis was hemangioma.

Treatment.—Between March 30, 1918, and Aug. 9, 1919, the patient received very heavy external irradiations and also moderate internal irradiations. The external irradiations consisted of 66,700 mc. hours of gamma radiation employed at a distance of 4 inches, distributed over both sides of the face and neck. The intranasopharyngeal treatment totaled 700 mc. hours of gamma radiation. Oct. 15, 1919, one needle point containing 4 mc. of radium emanation was implanted in the growth in the nasopharynx.

Course.—April, 1918, the patient was able to breathe through the right side of the nose, for the first time in a year.

October, 1918, the patient could breathe through both sides of the nose. The growth in the hard palate had not progressed.

January, 1919, the general condition was excellent, and the patient was able to breathe freely through the nose. There were no enlarged glands in the neck.

April, 1919, the growth in the nose was limited to the posterior half of the middle turbinate and the space between this and the inferior turbinate.

October, 1919, the general condition was excellent. The growth still remained in the posterior part of the nose on the left and in the nasopharynx; but there was no obstruction to breathing. There had been no bleeding during the previous year, and no metastatic glands were found.

CASE 10.—*History.*—A white woman, aged 47, was admitted in April, 1915, complaining of frequent and severe hemorrhages, eighteen months previously, also of a nasal obstruction on the right.

Examination.—The Wassermann reaction was negative. The adenoids had been removed thirty years previously. The general health had been excellent until the bleeding began, one and one-half years previously. The growth apparently originated from the region of the right middle turbinate, filling the entire nasopharynx. No metastatic glands were found, and the patient had no headache. A roentgen-ray examination of the chest was negative. The nature of the growth was recognized in New York, in March, 1914, and the patient was told that there was no hope for a cure by operation, but the use of radium was suggested.

Diagnosis.—A microscopic diagnosis proved the growth to be angiosarcoma.

Treatment.—The patient received intensive irradiation between March 29, 1915, and Oct. 11, 1916, a total of 27,800 mc. hours of gamma radiation being employed at a distance of 2½ inches over the right side of the face. She also received 500 mc. hours of gamma radiation directly against the growth in the right nostril. The patient reported regularly, and after Oct. 11, 1916, she

received several other radium treatments over the right side of the neck, which were given to reduce the adenoma of the thyroid, not affecting the condition in the nasopharynx.

Course.—April 10, 1915, there had been no bleeding during the previous week, which was very unusual. The patient could breathe through the right nostril freely, for the first time in months.

April 21, a metastatic growth had just appeared at the inner angle of the orbit on the right, measuring 1.5 by 0.75 cm.

July, 1915, the general health was excellent, with no further bleeding. There was no growth to be seen in the nose, in the nasopharynx or at the inner angle of the orbit. No enlarged glands were found.

October, 1915, there was a recurrence of the growth in the entire region of the middle turbinate on the right and at the inner angle of the orbit. The nasopharynx was free from growth. There were no enlarged glands.

November, 1915, there was no evidence of the growth in the nose, nasopharynx or orbit.

April, 1916, a second recurrence of the growth was found in the right nostril.

October, 1916, the nose, nasopharynx and orbit were free from any evidence of the growth; but there were dense adhesions in the upper part of the right nostril.

May, 1917, there was no evidence of any recurrence of the growth, and the general health was excellent.

August, 1920, the patient was perfectly well in every way.

January, 1922, the patient was healthy.

CASE 11.—*History.*—A white woman, aged 33, was admitted in October, 1915, complaining of a nasal obstruction of four years' duration, with frequent and profuse bleeding from the nose and throat. There had been exophthalmos and diplopia on the left. "Polypi" had been removed from the left side of the nose every two or three months from 1912 to 1915. During the early part of 1915, a nasal operation had been necessary every month, and recently, every week. On account of the appearance of exophthalmos, she was referred for radium treatment.

Examination.—The Wassermann reaction was negative. The glands in the neck were slightly enlarged on the left. The tissue which was removed at the various nasal operations had never been examined microscopically until her admission in October, 1915.

Diagnosis.—The microscopic diagnosis was angiosarcoma.

Treatment.—Intensive treatment was given the patient between Oct. 11, 1915, and Aug. 30, 1916, a total of 40,900 mc. hours of gamma radiation being employed at a distance of from 3 to 4 inches over the outside of both cheeks. In addition, she received 210 mc. hours of gamma radiation in the nasopharynx.

Course.—February, 1916, the diplopia had disappeared, and the exophthalmos was less marked. The left side of the nose was entirely filled with a soft, vascular growth.

August, 1916, the general condition was good, and the patient could breathe through the left side of the nose for the first time in a year.

September 1, there was a rapid recurrence of the growth both in the nose and nasopharynx, and the exophthalmos was also returning rapidly.

September 25, the patient's physician wrote that she was blind and unconscious and was dying rapidly. There was no necropsy.

CASE 12.—*History.*—A white man, aged 47, was admitted in May, 1912, complaining of a severe sore throat as the earliest symptom, nine months previ-

ously. During the first month, there was a rapid enlargement of the glands on both sides of the neck. He had difficulty in breathing through the nose, with tinnitus and impairment of hearing in the right ear and involvement of the third nerve on the right. The glands on both sides of the neck had been removed, six months previously, at the Newark City Hospital. The nose and throat were not examined at that time.

Examination.—There was no report of a Wassermann reaction. At this time, there was a recurrence of enlargement of the glands in the neck. The nasopharynx and the sphenoidal region on the right were entirely filled with growth.

Diagnosis.—The microscopic diagnosis was angiosarcoma.

Fig. 6.—Angiosarcoma involving antrum, orbit, right nostril and entire nasopharynx in a boy, aged 18 years; radium treatment; well three years later.

Treatment.—At this time (1912), no radium was available, and, on account of the recurrence of the enlargement of the glands in the neck and the evidence of orbital metastases, a surgical operation was not advised.

Course.—We have been unable to trace the patient; but this case is included in order to contrast the result with that in Case 1.

Case 13.—*History.*—A white boy, aged 18, was admitted in June, 1916. He had experienced difficulty in breathing through the right side of the nose, two years previously. There had been a purulent discharge from the right nostril for three months, with frequent hemorrhages from the nose and mouth. He also had a bilateral impairment of hearing, with exophthalmos on the right

and a swelling over the right antrum. The patient had had frequent nasal colds since early childhood. There was no history of headaches, nor of bleeding, and there was no metastasis to the glands in the neck.

Examination.—The Wassermann reaction was negative. The general condition was good; but the entire nasopharynx was filled with growth, including the right nostril and right antrum, not involving the hard palate.

Diagnosis.—The microscopic diagnosis was angioma or angiosarcoma.

Treatment.—Between June 21, 1916, and April 28, 1917, the patient had received heavy external irradiation over the outside of the right cheek, employed at a distance of from 2 to 5 inches, depending on the length of the individual treatments. The total treatment amounted to 53,300 mc. hours of gamma radiation. The most marked effect of the radium was the cessation of the spontaneous hemorrhages.

Course.—June 26, 1916, the first treatment, given five days previously, had resulted in a marked reduction in the size of the growth in the right nostril. There was a swelling over the right antrum; but the exophthalmos was much diminished.

June 28, the patient's face looked almost normal.

October, 1916, there was a recurrence of the swelling over the right side of the face, and the right nostril was filled with a sloughing tumor mass.

December, 1916, the general condition was improving; but there was no gain in weight. The right nostril and nasopharynx were filled with growth.

April, 1917, the local condition was about the same as at the last notation. The general condition was good, and no enlarged glands were found in the neck.

March, 1918, Dr. F. W. Janney reported that there was no evidence of a growth in the antrum, orbit, nose or nasopharynx. The middle turbinate on the right was enlarged, but otherwise appeared normal.

CASE 14.—*History.*—A white man, aged 26, was admitted in February, 1919, complaining of a nasal obstruction and a purulent discharge on the left, of three years' duration. He had had frequent and severe hemorrhages from the nose, and numerous nasal operations had been performed without relief of the symptoms.

Examination.—The Wassermann reaction was negative. There were moderately enlarged glands in the neck on the left, but none were palpable on the right. The right side of the nose appeared normal, while the left side of the nose and the left half of the nasopharynx were filled with growth. There was no ulceration and no trouble with the ears. A roentgen-ray examination of the chest proved negative.

Diagnosis.—The microscopic diagnosis was angioma.

Treatment.—Between Feb. 6, 1919, and Aug. 20, 1920, the patient received very intensive treatments, a total of 22,000 mc. hours of gamma radiation being employed at 4 inches, and 250 mc. hours of gamma radiation being used directly against the growth in the nasopharynx and a total of 16½ mc. of radium emanation in glass capillary points being implanted directly in the growth and left. This implantation treatment was equivalent to 1,850 mc. hours.

Course.—February, 1920, the condition in the left nostril and nasopharynx was about the same as in February, 1919. There was no evidence of any extension of the growth.

June, 1920, the growth had decreased in size, and the patient could breathe through the left nostril for the first time in four years. The enlarged glands in the neck on the left had disappeared.

October, 1920, the patient breathed freely through the left nostril but not so well through the right. There was still a tumor in the left nostril posteriorly, and also a globular tumor in the posterior nasopharynx. The patient had received tremendous treatment, and the result so far had been very good.

December, 1921, there had been no hemorrhages during the past year, and the growth had entirely disappeared from the nose and nasopharynx. Both sides of the nose appeared normal, with the exception of adhesions in the upper part of the left nostril. The general health was excellent. Subjectively and objectively, he seemed well.

LYMPHOSARCOMA OF THE NASOPHARYNX

CASE 15.—*History.*—A white man, aged 47, was admitted in March, 1914. The earliest symptom had been an obstruction of the left eustachian tube. The ear symptoms were thought to be due to hypertrophied adenoids, and from March, 1913, to January, 1914, the "adenoids" were removed five times under local anesthesia; but there had been a rapid recurrence. Although large masses of tissue had been removed from the nasopharynx on each occasion none of this tissue had been saved for examination. There was complete nasal obstruction in March, 1914. Enlarged glands had been found in the neck on the left, near the angle of the jaw. There had been no history of bleeding and no pain.

Examination.—The Wassermann reaction was negative. The growth was primary in the nasopharynx; it did not involve the nasal cavities, the soft palate, the orbit, the cranial cavity or any of the cranial nerves. The differential blood count was normal. There was no general glandular enlargement, and the abdominal organs were normal. A roentgen-ray examination of the chest was normal.

Diagnosis.—The microscopic diagnosis was lymphosarcoma (Fig. 7).

Treatment.—During March, 1914, the patient was given very mild radium treatment. March 4, 20, and 24, a total of 250 mc. hours of gamma radiation was employed in the nasopharynx, and 800 mc. hours was applied over the cervical glands, at a distance of 1 inch.

October, 1918, an exploratory operation was performed, and radium emanation was implanted in eight glass capillary points, in the abdominal growth. In addition to the radium treatment, the patient was treated with Fowler's solution for four years, according to a definite schedule. Every effort was made to keep him in the best possible physical condition.

Course.—March 4, 1914, 600 mg. of radium bromid was applied directly in the nasopharynx for one hour.

March 9, most of the growth had disappeared; but there was a large sloughing area in the nasopharynx. The patient could breathe freely through the nose for the first time in three months.

May 16, the nose, nasopharynx and eustachian tubes appeared normal, and there were no palpable glands in the neck. The general condition was excellent. For the next four years, the patient was examined every six months, and there never was any recurrence in the nose, throat or glands of the neck. He weighed 165 pounds.

October, 1918, the patient complained of a slight pain in the abdomen after eating, a swelling in the left side of the abdomen, and a loss of 10 pounds during the previous month. A large hard mass filled the entire left half of the abdomen. A roentgenogram of the chest revealed that the lungs and the mediastinum were normal.

October 25, an exploratory incision was made, with the implantation of radium points.

November 1, the abdominal tumor had entirely disappeared, i. e., it was no longer palpable.

November 16, there was a rapid recurrence, and the growth was felt in Douglas' pouch. At a second exploratory operation, disseminated nodules were found in the abdominal wound, and everywhere in the mesentery. No treatment was given.

Nov. 17, 1918, the patient died. Necropsy was not permitted.

Fig. 7.—Lymphosarcoma in a man, aged 47, which filled the entire nasopharynx and involved the cervical lymph glands; radium treatment; well for four years; growth then appeared in the retroperitoneal and mesenteric glands for the first time; disappeared after radium treatment but rapidly recurred; growth in nasopharynx and cervical glands never recurred during the four and one-half years of observation.

Case 16.—*History.*—A white girl, aged 17, was admitted in November, 1919, complaining of a nasal obstruction and a slight pain across the bridge of the nose. She had been operated on for the removal of tonsils and adenoids in June, 1916, which had relieved the nasal obstruction for one year; but it was

worse at the time of admission than ever before. There was no history of bleeding. The glands of the neck had not been involved.

Examination.—The Wassermann reaction was negative. The posterior half of the right nostril and the entire nasopharynx were filled with growth. There was no ulceration. All other examinations were negative.

Diagnosis.—The microscopic diagnosis was lymphosarcoma.

Treatment.—November, 1919: Between Nov. 8, 1919, and Sept. 20, 1920, the patient received very intensive irradiation, a total of 22,000 mc. hours of gamma irradiation being employed at a distance of from one-half to 3 inches over the right and left sides of the face, and 450 mc. hours of gamma radiation being used directly in the nasopharynx.

Feb. 26, 1920, the remains of the tumor in the nasopharynx were removed, and radium treatment was continued.

Course.—December, 1919, the growth was still present, but was much smaller, and the patient was able to breathe freely through the nose for the first time in two years.

February, 1920, there was no evidence of the growth in the nose; but it was still present in the nasopharynx. This was removed at operation.

March, 1920, there was a small nodule of the growth near the right eustachian tube; otherwise, the nose and the nasopharynx appeared normal.

June, 1920, there was no evidence of growth in the nose, nasopharynx or the glands of the neck. The general condition was excellent.

February, 1921, the general health was good, and there was no evidence of a recurrence, locally or elsewhere in the body.

CASE 17.—*History.*—A white woman, aged 35, was admitted in January, 1917, with a fractured nose, the result of an automobile accident, eight months previously, with an increasing nasal obstruction, and, recently, an impairment of hearing on the right and a nasal voice.

Examination.—The Wassermann reaction was negative. The growth apparently had originated in the posterior nasal cavity on the right, almost completely filling the nasopharynx. The orifice of the right eustachian tube could not be seen. The glands of the neck were just palpable on both sides. There was no bleeding and no pain.

Diagnosis.—The microscopic diagnosis was lymphosarcoma.

Treatment.—Between Feb. 3, 1917, and March 17, 1917, the patient received 22,400 mc. hours of external radiation, employed at a distance of 3 inches over the right and left sides of the face; 150 mc. hours of gamma radiation was used directly against the growth in the nasopharynx. In addition to the radium treatment, the growth was removed under ether anesthesia, and the nasal septum was straightened.

Course.—July, 1917, the nose and the nasopharynx appeared normal.

October, 1919, the patient was perfectly well. There were no palpable glands in the neck and no evidence of the growth.

October, 1920, the patient was perfectly well. The radium treatment did not affect the salivary glands.

January, 1922, the patient was well.

CASE 18.—*History.*—A white man, aged 45, was admitted in November, 1914, complaining of an impairment of hearing in the right ear. A growth, which was found to be the cause of the ear trouble, had been removed from the nasopharynx in June, 1913, followed by a rapid recurrence. No microscopic study

of the tissue was made and it was assumed to be syphilitic. He had been treated with silver, potassium iodid and arsphenamin, without any benefit. He had had a postnasal discharge for fifteen years. Operation had been performed on the sphenoids, ethmoids and antrums. He had severe tonsillitis in July, 1913, for eight weeks, losing 30 pounds in weight. A general enlargement of the glands occurred, the cervical and axillary glands on the right being as large as hickory nuts.

Examination.—The Wassermann reaction of both the blood and the spinal fluid was negative. The nasopharynx was entirely filled with growth, pushing the soft palate forward and involving the lateral pharyngeal wall on the right. The right side of the nose was also filled with growth. There was no infection in the ears, no pain and no bleeding. The differential blood count revealed: (1) increase in number of transitionals, 7.6 per cent.; (2) increase in number of platelets; (3) increase in number of eosinophils, 8 per cent.

Diagnosis.—The microscopic diagnosis was lymphosarcoma.

Treatment.—From Dec. 9, 1914, to Oct. 15, 1915, the patient received moderately heavy external irradiations, amounting to 9,200 mc. hours of gamma radiation employed at a distance of from 1 to 2½ inches, centered over the right and left sides of the neck, the right and left axillae and the right and left groins. He also received 130 mc. hours in the nasopharynx (screened with rubber).

Course.—Dec. 9, 1914, thirty-six hours after the first radium application, the patient was able to breathe through the left side of the nose for the first time in four months. On the third day, he could breathe through the right side of the nose for the first time in eighteen months. On the seventh day, the right eustachian tube opened, and the hearing returned to normal.

Jan. 8, 1915, there was no evidence of any growth in the nose or in the nasopharynx. The enlarged axillary and inguinal glands never decreased in size. It was thought that their enlargement was due to chronic skin diseases.

December, 1918, a letter stated that the patient died, December 21. No cause was given, and no necropsy was performed.

CASE 19.—*History.*—A white woman, aged 22, was admitted in December, 1916. She had been a mouth breather since early infancy, and had had frequent colds. The tonsils and adenoids had been removed in November, 1916. Two weeks later, a swelling had been noted—a tumor—in the soft palate on the left. The operative wounds had healed perfectly. The swelling of the soft palate had been thought to be due to infection, and was incised four days before admission. The fulness of the parotid region had been due to metastasis under the zygoma.

Examination.—The Wassermann reaction was negative. There was a large, hard, firmly fixed growth involving the soft palate on the left and the left lateral wall of the pharynx and nasopharynx, not involving the nose. This was all submucous. There was no ulceration, no otitis media. The differential blood count was normal, and the Pirquet reaction negative. The glands of the neck were not enlarged. There was no general glandular enlargement.

Diagnosis.—The microscopic diagnosis was lymphosarcoma (Fig. 8).

Treatment.—December, 1916, the large tumor mass in the soft palate and lateral wall of the pharynx was removed. After the overlying mucous membrane was split, the tumor mass shelled out very easily. The wound was left open, and radium was employed directly in the wound. No infection occurred, and after three weeks, the wound had healed. Between Dec. 16, 1916, and Jan.

23, 1918, the patient received very intensive radium treatments, consisting of 226,000 mc. hours of gamma radiation employed at a distance of from 3 to 5 inches over the right and left sides of the face. In addition, she received 350 mc. hours of gamma radiation, employed directly in the nasopharynx.

Course.—In April, 1917, the general condition was good, and there were no enlarged glands in the throat or the nasopharynx. The mass under the zygoma had disappeared.

June, 1917, there was a fulness of the lateral wall of the pharynx on the right and a recurrence of fulness under the zygoma on the left.

Fig. 8.—Lymphosarcoma in a girl, aged 2; well for eight months after combined operative and radium treatment; radium had no effect on the recurrent growth; arrangement of the cells suggests endothelioma. Compare with illustrations in an article by Pollak.[19]

July, 1917, there was no evidence of the growth anywhere.

October, 1917, there was a small mass surrounding the orifice of the left eustachian tube, and again there was a swelling under the left zygoma.

December, 1917, the growth has rapidly recurred in spite of the irradiation. There was a large mass in the left side of the pharynx, nasopharynx and the soft palate.

February, 1918, the patient died at home. No necropsy was performed.

CASE 20.—*History.*—A white girl, aged 10, was admitted in January, 1920. She had been easily fatigued during the previous year. The tonsils had been removed in September, 1919, because of pain in the joints. One month later, a swelling of the left side of the jaw and neck had been noticed. There had been no pain or bleeding, and the hearing had been gradually impaired on the left. A tumor, which had appeared following the removal of the tonsils and adenoids, had been found accidentally in the throat. She had gained 10 pounds since September, 1919, and now weighed 85 pounds.

Examination.—The Wassermann reaction was negative. There was a swelling of the left half of the soft palate and of the left posterior pillar, involving the entire nasopharynx. The voice was nasal. The anterior nares were normal. A roentgenogram of the chest was normal. There was no general glandular enlargement. The glands were enlarged at the angles of the jaw, but more on the left, with a fulness over the left side of the face. The Pirquet reaction was negative. There was postural albuminuria (?), and secondary anemia.

Diagnosis.—No tissue was removed for a microscopic examination; but the clinical diagnosis was lymphosarcoma.

Treatment.—Between Jan. 7, 1920, and Feb. 14, 1920, the patient received 9,000 mc. hours of gamma radiation, from a distance of 3 inches, centered over the left side of the neck. There was no evidence of growth at the latter date. She was given very heavy irradiation over the occipital region and over the right femur between September 6 and 12, 1920.

Course.—March, 1920, all evidence of the growth had disappeared from the mouth, and there were no enlarged glands in the neck. A small amount of tissue in the midline of the nasopharynx was seen that grossly resembled adenoid tissue. The eustachian orifices were clear.

June, 1920, the patient was subjectively well. She had a clear voice; the pharynx and the nose were normal, and examination of the ears was negative. Adenoid tissue appeared to be present in the nasopharynx, and there were some adhesions between this and the eustachian tube on the right.

September, 1920, there were metastasis to the brain, choked disk and strabismus. A roentgenogram of the femur revealed the periosteum lifted and thickened. The patient died, and no necropsy was performed.

CASE 21.—*History.*—A white girl, aged 14, was admitted Feb. 23, 1918. A lump had been noticed in the soft palate in December, 1917. Three weeks before admission, she had had her tonsils removed, and ten days later, there had been a rapid increase in the size of the growth.

Examination.—A tumor was visible when the soft palate was lifted; but the eustachian tube and the glands of the neck were not involved. There was no history of bleeding.

Diagnosis.—The microscopic diagnosis was lymphosarcoma.

Treatment.—Between Feb. 23, 1918, and March 30, 1918, the patient received very intensive irradiation, as much as could be employed with safety during this short period. A total of 64,700 mc. hours of gamma radiation from a distance of 5 inches was centered over the right and left sides of the neck, and one treatment was also given over the metastasis in the lower abdomen. In addition, she received very mild treatment in the pharynx.

Course.—March 2, 1918, the growth had almost entirely disappeared, and no palpable glands were found in the neck.

March 7, 1918, the growth in the soft palate was about 1 cm. in diameter.

March 15, 1918, there was a rapid recurrence, and the growth was almost as large as on admission.

March 28, 1918, there was a large mass in the left lower part of the abdomen, the size of an egg, also an evidence of metastasis to the liver.

June, 1918, the patient died, and no necropsy was performed.

CASE 22.—*History.*—A white woman, aged 23, was admitted in December, 1916. The earliest symptom had been impairment of hearing on the left, which had occurred six months previously. The glands on the left side of the neck were enlarged. She suffered pain in the left side of the head as well as in the teeth on the left.

Examination.—The Wassermann reaction was negative. The growth originated from the vault and the left lateral wall of the nasopharynx. The mucous membrane over it was intact. There was no history of bleeding. A roentgenogram of the sinuses and chest was negative, and the blood count was normal.

Diagnosis.—No tissue was removed for a microscopic examination; but the clinical diagnosis was lymphosarcoma.

Treatment.—Between Dec. 27, 1916, and June 5, 1917, the patient received very intensive irradiation, an external treatment of 81,800 mc. hours of gamma radiation being employed at 3 inches over the right and left sides of the face, and light treatments being given in the nasopharynx, totaling 120 mc. hours of gamma radiation.

Course.—January, 1917, the patient had gained 11 pounds in weight. The glands of the neck were smaller, and the hearing on the left was normal.

February, 1917, the growth in the nasopharynx had disappeared, and the glands were just palpable.

June, 1917, no evidence of the growth was seen in the nose or throat. The glands were not palpable.

July 16, 1920, the patient wrote that she was in splendid health, looked well and that there was no evidence of any return of the trouble. She weighed 139 pounds.

June, 1922, the glands in the neck had recurred, and she had a septic temperature. The patient was receiving radium treatment from Dr. C. J. Miller of New Orleans.

CASE 23.—*History.*—A white man, aged 71, was admitted Feb. 7, 1918, complaining of a sore throat of four months' duration, and pain on swallowing for the previous ten days. He had been given arsphenamin without any improvement, and had lost 20 pounds during the past four months.

Examination.—The Wassermann reaction was negative. The entire nasopharynx was filled with a mass which had largely destroyed the soft palate and the left tonsil, the cavity being the size of a hen's egg. He had had frequent attacks of sore throat for fifteen or twenty years, which became worse every year.

Diagnosis.—The microscopic diagnosis was lymphosarcoma.

Treatment.—Between Feb. 7, 1918, and July 26, 1918, the patient received intensive irradiation, both from the outside and in the nasopharynx, a total of 47,200 mc. hours of gamma radiation, at a distance of from 3 to 5 inches, being employed over the right and left sides of the neck, and 450 mc. hours directly against the tumor.

Course.—Feb. 21, 1918, the patient was improved, and the growth in the throat was smaller.

Feb. 27, 1918, he was able to swallow with less pain.

March 27, 1918, the patient had improved wonderfully, and the growth in the throat was nearly gone.

April 27, 1918, the tumor was smaller, owing to the heavy irradiations given every other day.

May 14, 1918, the general condition was excellent; but there was still a little thickening on the left side of the soft palate.

May 28, 1918, the growth was beginning to recur, and the radium treatments inside the mouth caused a great deal of irritation, without seeming to cure.

June 15, 1918, no enlarged glands were found in the neck; but there was considerable growth in the pharynx.

July 8, 1918, the glands were just palpable in the posterior triangles of the neck. There was a large growth in the nasopharynx, which covered the left eustachian tube and extended down the left lateral wall of the pharynx, involving the tonsil, soft palate, base of the tongue and the epiglottis. Both sides of the nose appeared normal.

October, 1918, the patient died, and no necropsy was performed.

Case 24.—*History.*—A white man, aged 22, was admitted in December, 1920, complaining of a nasal obstruction, of four months' duration, and pain in the left side of the face and in the upper and lower teeth, as well as frontal headache. There had been no history of bleeding either from the mouth or the nose. There was jaundice and a severe pain referred to the lower dorsal and upper lumbar regions. A roentgenogram of the spine was negative.

Examination.—The Wassermann reaction was negative. The glands were just palpable on both sides of the neck. The growth apparently arose from the posterior part of the septum on the left, filling the entire nasopharynx. There was a slight exophthalmos on the left and also an impairment of the sensation of the second and third division of the trigeminus on the left, the impaired hearing being due to the eustachian tube obstruction. The blood count was: leukocyte, 9,000; eosinophils, 0.5 per cent.; lymphocytes, 11 per cent.; differential count: mononuclears, 6.5 per cent.; polymorphonuclears, 81.5 per cent.; basophils, 0; platelets, slightly increased.

Diagnosis.—The microscopic diagnosis was lymphosarcoma.

Course.—Dec. 18, 1920, 3,930 mc. at 5 inches was applied for two hours over each side of the face.

Dec. 24, 1920, 3,849 mc. at 5 inches was applied for one and one-half hours over each side of the nose. The patient returned to the Walter Reed Hospital where he died Feb. 5, 1921.

Necropsy.—The growth had invaded the left frontal sinus, ethmoids, orbit and antrum. The left sphenopalatine ganglion was surrounded with growth. The mediastinum was not involved. There were no liver or kidney metastases. A metastatic growth was found in the head of the pancreas, causing almost complete obstruction of the common duct. An examination of the gastrointestinal tract was negative. There were no metastases to the brain.

Comment.—The irradiation in this case did not result in any evident decrease in the size of the nasopharyngeal growth. The necropsy revealed that the tumor involved the ethmoidal region, frontal sinus, orbit and sphenopalatine fossa on the left. The tumor of the nasopharynx and accessory sinuses showed great masses of lymphocytic cells with relatively large, densely staining nuclei, sur-

rounded by a narrow zone of neutral staining cytoplasm. The stroma was scant and delicate in structure. The cell masses came up to the epithelium but did not appear to invade or destroy it. Sections showed bone, however, being destroyed. The diagnosis was lymphosarcoma of the lymphocyte cell type (Paul A. Schule, Chief, Laboratory Service, Walter Reed General Hospital).

OTHER TYPES OF SARCOMA OF THE NASOPHARYNX

CASE 25.—*History.*—A white boy, aged 4½ years, was admitted in December, 1917, complaining of nasal obstruction and discharge from the ears, but no bleeding. The growth in the nose had first been noticed six months previously, one month after removal of the tonsils and adenoids.

Examination.—The Wassermann reaction was negative. The growth had apparently originated in the nasopharynx and had grown rapidly into both nostrils and downward into the pharynx, resulting in complete nasal obstruction and great difficulty in breathing through the mouth. The glands of the neck were not involved.

Diagnosis.—The microscopic diagnosis was spindle-cell sarcoma (Fig. 21).

Treatment.—On two occasions it was necessary to remove the growth from the pharynx so that the child could breathe through the mouth and swallow. Large doses of radium were applied directly to the base of the growth at each operation. Between Oct. 3, 1917, and Dec. 22, 1917, the patient received very intense irradiation. A total of 37,600 mc. hours of gamma radiation was applied over the right and left sides of the face at a distance of 4 inches. In addition, 150 mc. hours of gamma radiation was applied directly in the nasopharynx against the tumor.

Course.—December, 1917: Before admission to the hospital, the patient had received fourteen radium treatments, with the result that for a time the growth had entirely disappeared. It rapidly recurred, and after admission the growth was removed and 500 mc. of radium was applied directly on the points of attachment of the growth for two minutes in five areas (in all a total of ten minutes). The growth recurred within two weeks. Heavy external irradiation was employed and again radium was applied directly to the growth in several areas (542 mc. for a total of ten minutes).

January, 1918, the growth had not disappeared from the nasopharynx; but it was no longer visible in the mouth or in either side of the nose. Two hundred and seventy-nine mc. of radium was applied directly on the growth in the nasopharynx for sixteen minutes. There were no enlarged glands in the neck.

March, 1918, the patient died. The growth rapidly recurred and radium had no effect. The orbit and the intracranial cavity were invaded.

CASE 26.—*History.*—A white man, aged 51, was admitted in November, 1914, complaining of difficulty in breathing through the nose and a muffled voice of three months' duration. There had been no bleeding.

Examination.—The Wassermann reaction was negative. The growth had originated on the posterior part of the septum or in the nasopharynx. It was smooth, hard and covered with intact mucous membrane. The glands of the neck were not enlarged.

Diagnosis.—The microscopic diagnosis was spindle-cell sarcoma (alveolar arrangement, Fig. 9).

Treatment.—The patient received mild external irradiation, Jan. 26, 1915, 6,100 mc. hours of gamma radiation being employed at a distance of 2 inches.

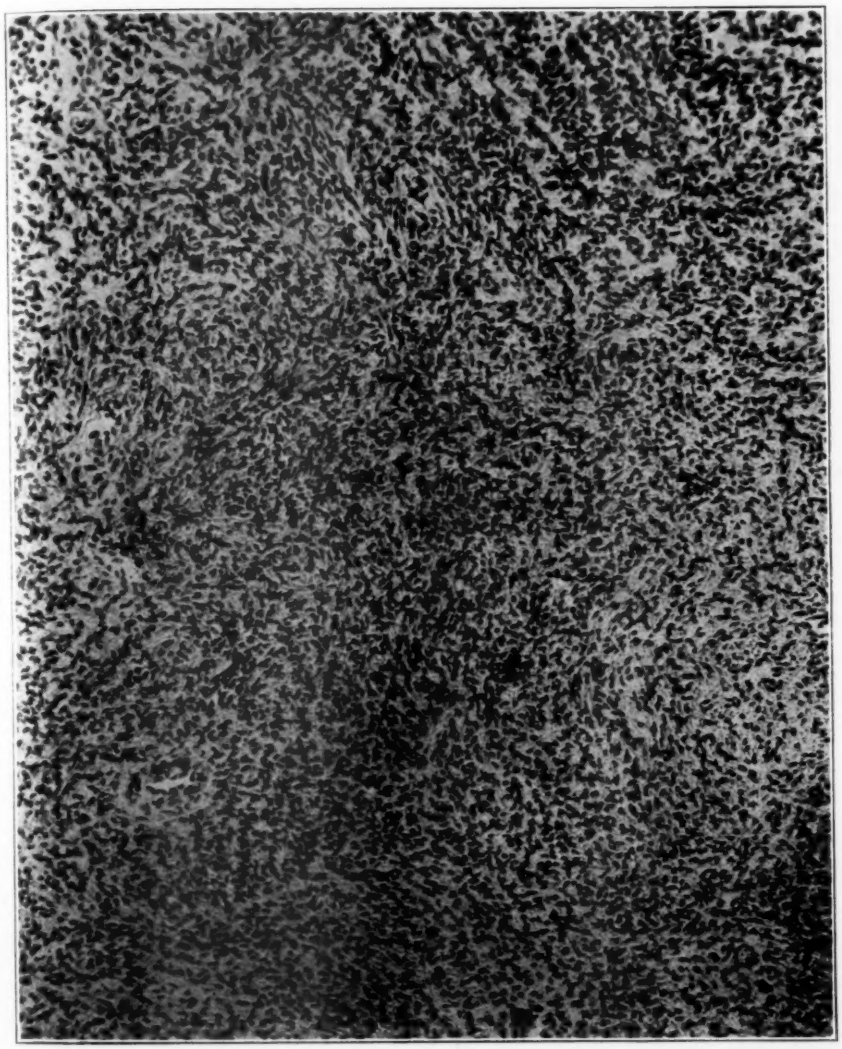

Fig. 9.—Spindle-cell sarcoma in a man, aged 51, whose chief symptom was nasal obstruction; after irradiation there was marked improvement for six months; then rapid recurrence and intracranial invasion; alveolar arrangement may be noted.

February 20, 564 mc. hours of gamma radiation was applied directly in the nasopharynx. March 29, 1,000 mc. hours of gamma radiation was applied directly in the growth by implantation.

Course.—February, 1915, the radium had had little effect on the growth in the nasopharynx. The growth involved the right side of the nose and had destroyed the vomer. The patient was suffering severe pain.

July, 1915, there was fixation of the jaw, as well as intracranial and orbital involvement, abducens paralysis and visual disturbances. The growth had involved the right antrum, ethmoids and sphenoid. The patient died.

Case 27.—*History.*—A white boy, aged 16, was admitted in June, 1918, complaining of nasal obstruction of one and one-half years' duration. He had had no headache, no ear symptoms, and there was no history of bleeding.

Examination.—The Wassermann reaction was negative. The growth had apparently originated just below the posterior end of the middle turbinate on the left. It filled the nasopharynx and caused obstruction of the right nostril by pushing the septum over. There was no tumor in the right nostril. The glands of the neck were palpably enlarged on both sides.

Diagnosis.—The microscopic diagnosis was myxosarcoma (Fig. 10).

Treatment.—Between June 27, 1918, and March 13, 1920, the patient received very intensive irradiation externally, applied to both sides of the head at a distance of from 2 to 5 inches, totaling in all 83,000 mc. hours of gamma radiation applied directly to the surface of the growth by inserting emanation tubes into the nasopharynx, and a total of 1,800 mc. hours of gamma radiation applied by inserting two capillary tubes, each containing 5 mc. of radium emanation, into the tumor in the nasopharynx. The details of the radium treatment in this case are given in the accompanying table.

Course.—September, 1918, the growth had greatly decreased in size.

April, 1918, the patient had had twenty-eight radium treatments, both intranasal and external, with but little permanent improvement. The nasal obstruction still remained.

May, 1919, the patient had gained 6 pounds in weight.

August, 1919, the growth had decreased in size again.

November, 1919, the growth in the nose and nasopharynx was sloughing. The glands in the neck were about the size that they were a year previously. The soft palate was perforated on the left side as a result of a radium burn.

March, 1920, the patient was much improved. The growth had disappeared from the left side of the nose and from the left side of the nasopharynx. The orifice of the right eustachian tube was still obscured by growth.

June, 1920, there was no growth in the nose. There was still a small growth in the right side of the nasopharynx. The patient breathed normally through the nose.

Aug. 17, 1921, there was slight irritation in the nasopharynx on the left side, but no growth whatever. There was a hole in the soft palate which interfered with phonation.

Case 28.—*History.*—A white man, aged 24, was admitted in May, 1918, complaining of nasal obstruction of six months' duration. There was impaired hearing, owing to obstruction of both eustachian tubes, but no history of bleeding.

Examination.—The Wassermann reaction was negative. There was a retropharyngeal growth covered with smooth mucous membrane visible in the mouth.

DETAILED NOTES OF RADIUM TREATMENT IN CASE 27

Date	Dosage Mg.	Distance	Site of Application	Duration of Application
June 27, 1918	3657	6 in.	Left side of nose	1 hour
June 30, 1918	3629	6 in.	Left side of nose	3 hours
July 3, 1918	3374	5 in.	Both sides of nose	1 hour
July 10, 1918	3657	4 in.	Left side of nose	2 hours
July 14, 1918	2714	4 in.	Left side of nose	2 hours
July 17, 1918	4009	4 in.	Left side of nose	2 hours
July 21, 1918	3921	4 in.	Left side of nose	1 hour
July 25, 1918	3695	5 in.	Left side of nose	1 hour
July 28, 1918	3225	5 in.	Left side of nose	1 hour
Aug. 1, 1918	4093	5 in.	Left side of nose	1 hour
Sept. 13, 1918	3046	3 in.	Both sides neck	Total 1½ hours
	500	....	Direct in each nostril	4 min.
Sept. 16, 1918	3006	3 in.	Over angles of jaw	45 minutes each
Sept. 20, 1918	3651	3 in.	Over angles of jaw	45 minutes each
Sept. 24, 1918	2824	3 in.	Over angles of jaw	30 minutes each
Nov. 30, 1918	378	....	Direct to growth	10 minutes
Dec. 3, 1918	423	....	Direct to growth	10 minutes
Dec. 4, 1918	353	....	Direct to nose	5 minutes
Dec. 6, 1918	245	....	Direct to nose	5 minutes
Dec. 9, 1918	773	3 in.	To nose	One-half hour
Dec. 10, 1918	282	....	Direct to nose	10 minutes
Dec. 11, 1918	2981	4 in.	To nose	2 hours
Dec. 13, 1918	2101	3 in.	To nose	15 minutes
Mar. 9, 1919	1042	....	Direct to nasopharynx	4 minutes
Mar. 11, 1919	774	....	Direct inside nose	6 minutes
Mar. 15, 1919	883	....	Direct inside nose	6 minutes
Mar. 13, 1919	1348	....	Direct inside nose	6 minutes
Mar. 26, 1919	972	....	Direct inside nose	4 minutes
Mar. 30, 1919	874	....	Direct inside nose	4 minutes
Apr. 1, 1919	945	....	Direct in nose	4 minutes
Apr. 4, 1919	675	....	Direct inside nose	3 minutes
Apr. 7, 1919	395	....	Direct inside nose	5 minutes
Apr. 9, 1919	855	....	Direct inside nose	6 minutes
Apr. 11, 1919	1046	....	Direct in nasopharynx	3 minutes
Apr. 14, 1919	876	....	Direct in nasopharynx	4 minutes
Apr. 16, 1919	903	....	Direct in nasopharynx	3 minutes
Apr. 18, 1919	583	....	Direct in nasopharynx	4 minutes
Apr. 21, 1919	364	....	Direct in nasopharynx	5 minutes
Apr. 23, 1919	938	....	Direct in nasopharynx	3 minutes
Apr. 27, 1919	858	....	Direct in nose	4 minutes
Apr. 29, 1919	1167	....	Direct in nose	3 minutes
May 1, 1919	811	....	Direct in nose	4 minutes
May 3, 1919	563	....	Direct in nose	4 minutes
May 5, 1919	391	....	Direct in nose	5 minutes
May 7, 1919	973	....	Direct in nose	3 minutes
May 9, 1919	675	....	Direct to throat	2 minutes
May 19, 1919	372	....	Direct to nasopharynx	3 minutes
May 21, 1919	973	....	Direct inside nose	1 minute
May 23, 1919	670	....	Direct to nasopharynx	2 minutes
Aug. 9, 1919	485	....	Direct to nasopharynx	5 minutes
Aug. 12, 1919	280	....	Direct to inside of nose	5 minutes
Aug. 15, 1919	682	....	Direct to inside of nose	5 minutes
Aug. 18, 1919	404	....	Direct to nasopharynx	5 minutes
Aug. 21, 1919	One 4 mc.		Needle implanted into pharynx	
Dec. 1, 1919	One 5 mc.		Needle inserted in growth through nose	
Mar. 13, 1920	872	....	Direct to nasopharynx	13 minutes

SUMMARY:

Total Treatments:

14½ gr. hrs. at 6 inches
18 gr. hrs. at 5 inches
30½ gr. hrs. at 4 inches
18¼ gr. hrs. at 3 inches
1⅓ gr. hrs. direct
9 mc. implanted in growth.

The growth did not involve the nasal cavities. The glands of the neck were enlarged on the right (metastatic), but smaller on the left. There was no evidence of orbital or intracranial involvement. The differential blood count was normal.

Diagnosis.—The microscopic diagnosis was round-cell sarcoma.

Treatment.—Between May 18, 1918, and Jan. 28, 1919, intensive radium treatment was given, consisting of 72,700 mc. hours of gamma radiation at 5 inches,

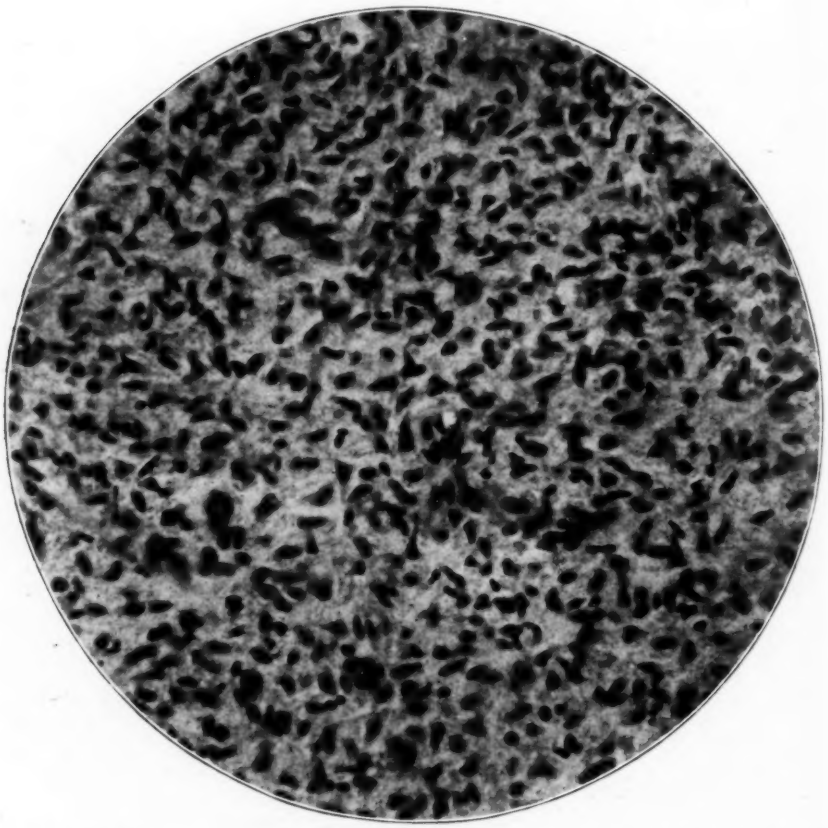

Fig 10.—Myxosarcoma of the nose and nasopharynx in a boy, aged 16; complete nasal obstruction for one and one-half years before irradiation; well three years later.

centered over the right and left sides of the face. He also received 480 mc. hours of gamma radiation in the nasopharynx.

Course.—June, 1918, there was no improvement.

October, 1918, the glands in the neck had almost disappeared. The growth in the nasopharynx was much smaller, and the patient had gained in weight.

April, 1919, cachexia was present. The patient had been much worse during the previous three months. Enlargement of the glands in the neck had recurred. There was weakness of the left facial and spinal accessory nerves. A roentgenogram revealed small mediastinal glands for the first time.

October, 1919, the patient died. The growth had apparently involved the cervical spine and had caused complete paralysis.

CASE 29.—*History.*—A white boy, aged 16, was admitted in May, 1919, complaining of nasal obstruction. He had had several nasal operations during the previous year. The glands in the neck were not enlarged.

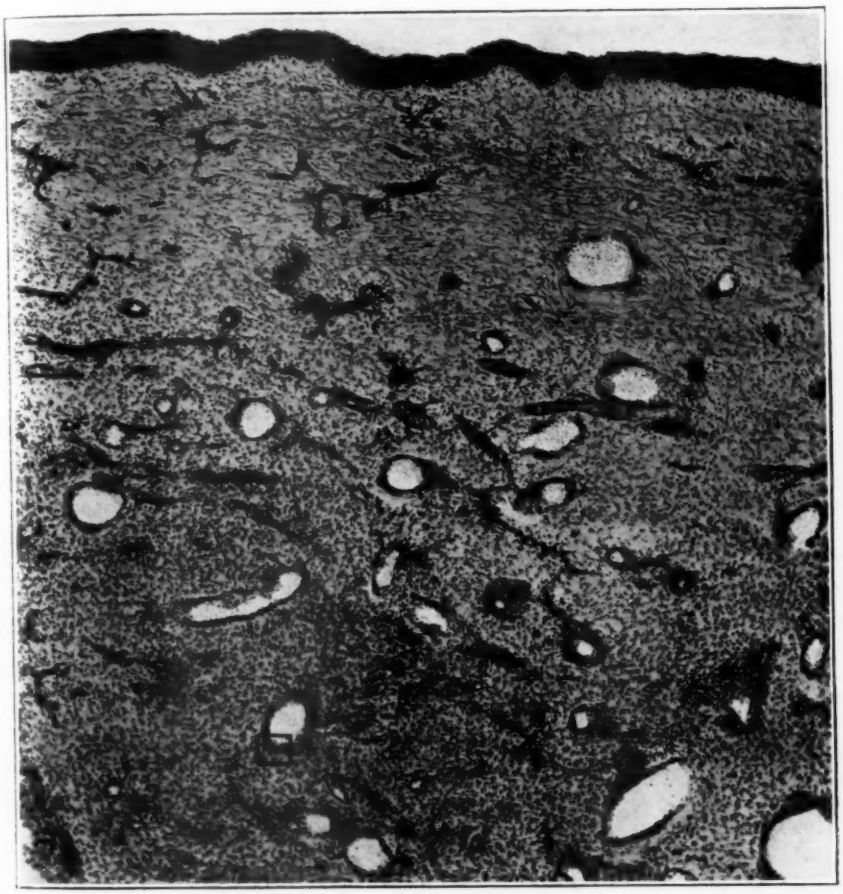

Fig. 11.—Myxosarcoma of the nose and nasopharynx in a boy, aged 16; complete nasal obstruction for one year; no improvement following radium treatment; section comes from the posterior end of the inferior turbinate; area marked is shown in Figure 12.

Examination.—The Wassermann reaction was negative. The growth filled the entire nasopharynx and both sides of the nose. There was involvement of the right antrum nine months after the onset of symptoms.

Diagnosis.—The microscopic diagnosis was myxosarcoma (Figs. 11 and 12).

Treatment.—Between June 13, 1919, and Aug. 26, 1919, the patient received three heavy irradiations at a distance of from 5 to 6 inches. The total radiation

amounted to 46,500 mc. hours of gamma radiation applied intensively during the time that it was given.

Course.—August, 1919, there was no improvement. The growth extended under the malar arch on the right. The patient died.

CASE 30.—*History.*—A colored man, aged 49, was admitted in April, 1918, complaining of nasal obstruction on the right, headaches and nosebleed, the onset of which had occurred six months previously.

Examination.—The Wassermann reaction was negative. The growth arose from the lateral nasal wall on the right. The left nostril and the nasopharynx

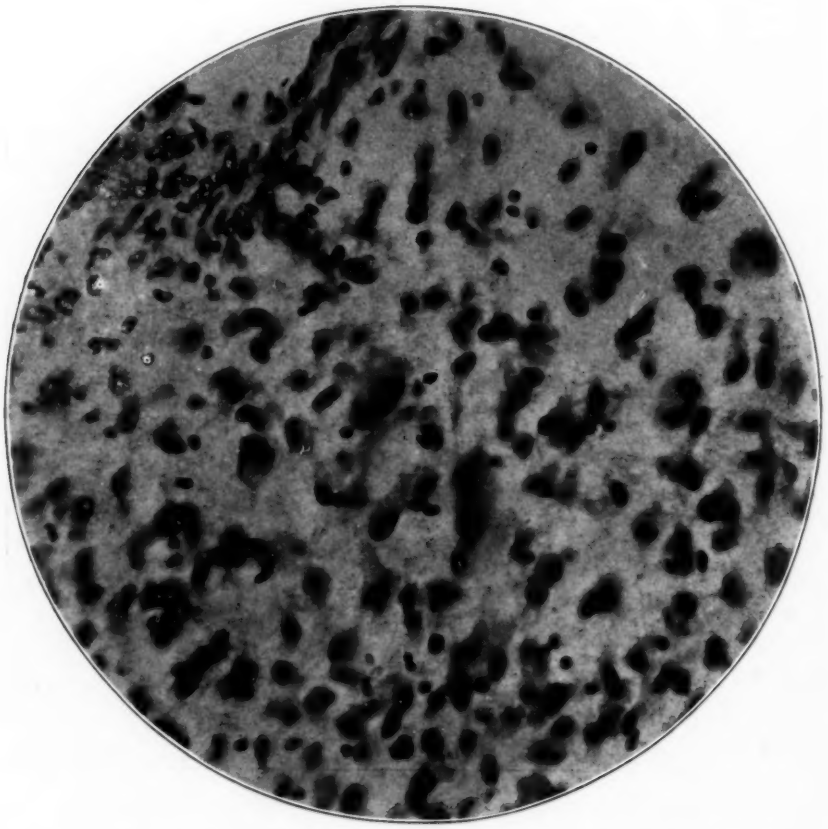

Fig. 12.—Portion of specimen shown in Figure 11, illustrating the type of tumor cell. This patient died. Compare with Figure 10.

were not involved. The nose bled easily. There were no enlarged glands in the neck, and no ear symptoms. The roentgen ray revealed clouding of the right antrum, suggesting growth.

Diagnosis.—The microscopic diagnosis was sarcoma.

Treatment.—The patient was given very intensive irradiation between April 30, 1918, and Dec. 5, 1919. The external irradiations totaled 31,300 mc. hours of gamma radiation at a distance of 4 inches over the right and left sides of the

face. In addition to this, he received a total of 71 mc. of radium emanation in glass capillary tubes, in amounts varying from 3 to 7 mc., all implanted directly into the nasopharynx.

Course.—April 27, 1919, there was no improvement in the breathing space.

September, 1919, there was still a large growth in the right nostril, and bleeding was less frequent.

February, 1920, the right nostril was entirely occluded.

CASE 31.—*History.*—A white woman, aged 47, was admitted in April, 1915, complaining of enlarged glands in the neck and difficulty in breathing, even

Fig. 13.—Sarcoma of the nasopharynx in a man, aged 49; history of nasal obstruction, pain and frequent hemorrhages. Radium did not cause the growth to disappear, but the symptoms are relieved and the growth has not advanced during the two years of observation.

through the mouth. The onset of symptoms had occurred seven months before admission.

Examination.—There were metastatic glands in the neck on both sides. The entire soft palate was pushed forward by a large soft reddish growth. There was no general glandular enlargement, no bleeding and no ear symptoms. A roentgenogram of the chest revealed no definite changes.

Diagnosis.—The microscopic diagnosis was round-cell sarcoma.

Treatment.—Between April 10, 1915, and June 20, 1916, the patient was given very extensive external irradiation, 45,000 mg. hours of gamma radiation being employed at a distance of 2 inches.

Course.—April 16, 1915: The first radium treatment was given five days previously.

May, 1915, the growth had decreased to one-third its original size. There was no growth in the throat. There was one large mass of glands in the right side of the neck, measuring 5 by 5 cm.

August, 1915, the patient felt better. There was no difficulty in breathing. One small gland was felt in the neck. She had gained in weight.

September, 1915, a large gland was present on each side of the neck.

Oct. 2, 1915, the gland on the right side of the neck had disappeared. The one on the left was smaller.

October 23, the gland in the right axilla was enlarged.

January, 1916, there was general glandular enlargement, a mass in the upper part of the abdomen on the left, and a recurrence in the throat.

April 14, 1916, the patient died, having been confined to her bed for the previous year. The glands of the neck had broken down.

CASE 32.—*History.*—A colored man, aged 48, was admitted in March, 1915, complaining of symptoms that had occurred seven months previously. The first symptom was obstruction of the tear duct on the right, then exophthalmos and nasal obstruction on the right. There had been no pain.

Examination.—The Wassermann reaction was negative. The growth had apparently originated in the ethmoidal region on the right, later involving the nasopharynx. There had been no pain during the first year of the trouble. There were no palpably enlarged glands at the time of examination. There was no bleeding at any time.

Diagnosis.—The microscopic diagnosis was sarcoma.

Treatment.—Oct. 1, 1920, the patient received intensive irradiation, 37,000 mc. hours of gamma radiation being employed at a distance of 2 inches. Light radiation was also applied directly to the growth by means of a sound inserted through the nostril.

Course.—May, 1915, the growth had markedly decreased in size. Exophthalmos was less marked. The patient could now breathe easily through the nose, although it still contained a visible growth.

June, 1915, there was no further improvement.

September, 1915, there were large masses of metastatic glands on both sides of the neck. The nasopharynx and the left side of the nose were involved. The general condition was worse.

June, 1916, the patient died of intracranial involvement, terminating in meningitis.

CASE 33.—*History.*—A white boy, aged 19, was admitted in May, 1918, complaining of obstruction to breathing through the nose as the earliest symptom, one year previously. A large mass of "adenoids" had been removed in August, 1917, but was not examined microscopically. Since this operation frequent and severe hemorrhages had been the most prominent symptom. In April, 1918, the growth in the nasopharynx was again removed, after a preliminary tracheotomy. Recurrence had been rapid.

Examination.—The Wassermann reaction was negative. Both sides of the nose posteriorly and the entire nasopharynx were filled with growth. The soft palate was pushed forward by the growth.

Diagnosis.—The microscopic diagnosis was myxosarcoma.

Treatment.—The patient received intensive treatment between May 1, 1918, and Dec. 6, 1920. During this time, 16,950 mc. hours of gamma radiation was applied directly to the growth at a distance of from 1 to 5 inches; 37 mc. was implanted in the growth.

Course.—July, 1918, an emanation point was buried in the nasopharynx.

September, 1918, the growth was steadily diminishing in size. Hemorrhages were less frequent.

January, 1919, the growth had almost disappeared from both sides of the nose. There were remains of the growth in the nasopharynx. The patient could breathe through the nose.

March, 1919, the growth remained about the same in the nasopharynx. The general health was excellent. Radium was applied directly to the tumor through each nostril and through the mouth. This treatment was followed within a few days by a severe hemorrhage.

June, 1919, the growth in the nasopharynx was much larger and had recurred in the left side of the nose. There was profuse bleeding after each treatment.

June, 1920, the growth was much smaller than it had been a year previously. The patient breathed well through the nose. Bleeding was much less frequent.

April 23, 1921, the patient was seen by Dr. Winslow, who found no evidence of trouble. Dr. William Neill, Jr., in his examination, concurred with Dr. Winslow. He pronounced it a perfect result, and, in spite of the heavy implantation and direct application, there was no damage to the soft palate or septum.

May 11, 1922, the patient felt perfectly well. Examination of the nasopharynx by Dr. C. F. Burnam revealed a perfectly normal condition.

CARCINOMA OF THE NASOPHARYNX

CASE 34.—*History.*—A white man, aged 23, was admitted, Nov. 30, 1914, complaining of pain in the throat and swelling of the glands of the neck, nasal obstruction on the left, headache and nosebleed, and fixation of the jaw. These symptoms had been of four months' duration.

Examination.—The Wassermann reaction was negative. The obstruction of the posterior part of the nose on the left was due to the growth. There were no ear symptoms. There were metastatic glands on both sides of the neck.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—The patient received a moderate single radium treatment, Dec. 6, 1914, 3,800 mc. hours of gamma radiation being employed at a distance of 1 inch. There were no other treatments, and the radium treatment in this case can hardly be considered.

Course.—There were no subsequent notes.

CASE 35.—*History.*—A white woman, aged 42, was admitted in February, 1919, complaining of sore throat, bleeding from the throat and enlarged glands of the neck on both sides. The glands of the neck on the right were as large as an orange, and those on the left were visibly enlarged.

Examination.—The Wassermann reaction was negative. The growth arose from the vault and the right lateral wall of the nasopharynx. The nose was not involved. There was no obstruction to breathing and no ear symptoms. There were huge glands in the neck.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—Between Jan. 17 and Sept. 11, 1920, the patient received very intense irradiation, 22,900 mc. hours of gamma radiation, at a distance of 2 inches, being employed over the right side of the face and neck. Fourteen mc. of radium emanation was also implanted directly into the involved glands in the neck and 500 mc. of gamma radiation was implanted directly in the nasopharynx. In October, 1919, a portion of an enlarged gland of the neck on the left was removed for microscopic examination. Nov. 20, 1919, the glands of the neck on the right were excised. Operation for excision of the glands on the left was refused. No operation was performed on the nasopharynx.

Course.—January, 1920, the general condition was excellent. There was a recurrence in the glands high up on the right side of the neck. Radium was implanted in these glands in June, 1920. The glands of the neck were not palpably enlarged. The patient was gaining in weight.

October, 1920, examination revealed no evidence of growth in the nasopharynx. The patient was breathing freely.

October, 1921, the patient died with involvement of the mediastinum and esophagus. There was no recurrence in the nasopharynx.

Case 36.—*History.*—A white girl, aged 19, was admitted in August, 1919, complaining of enlarged glands of the neck on the left, inability to open the mouth and bleeding from the mouth. The symptoms had been present for three months.

Examination.—The Wassermann reaction was negative. The growth arose in the nasopharynx on the left. The nose was not involved. There was no obstruction, no bleeding and no ear symptoms.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—The patient would not consent to radium treatment for four months after the diagnosis had been made.

Dec. 2, 1919, the patient received 200 mc. hours of gamma radiation applied directly against the growth in the nasopharynx, also two external irradiations, Dec. 7 and Dec. 14, 1919, totaling 6,800 mc. hours, centered over the glands of the neck. This was very mild irradiation.

Course.—July, 1920, cachexia had developed, and the patient was confined to bed. There were frequent hemorrhages from the throat.

Case 37.—*History.*—A white woman, aged 33, was admitted, April 18, 1917, complaining of headache, bleeding from the throat, enlarged glands of the neck, fixation of the jaw and loss of the sense of smell. The patient was also suffering from agitated depression, for which she had been admitted to the Phipps Psychiatric Clinic. The adenoids had been removed in September, 1916, because of bleeding. The tonsils had been removed, March 19, because of cervical adenitis. The tissue was not examined microscopically. Examination by Dr. Harvey Cushing for brain tumor, in April, 1916, was negative.

Examination.—The Wassermann reaction was negative. There were metastatic glands on both sides of the neck, diplopia, but no otitis media.

Diagnosis.—The microscopic examination of tissue removed from the nasopharynx was carcinoma.

Treatment.—Sept. 22, Oct. 22 and Nov. 14, 1917, a radium treatment was applied to the glands of the neck. Oct. 4 and Nov. 24, 1917, an external treatment was given. October, 1917, 600 mg. of radium emanation was applied to the right side of the nasopharynx for ten minutes and to the left side for five minutes. November, 1917, 850 mg. was applied for five minutes each: (1) over the anterior portion of the left sphenoid; (2) over a portion of the right sphenoid; (3) and (4) against each pharyngeal wall.

Course.—Dec. 22, 1917, the patient died of intracranial involvement.

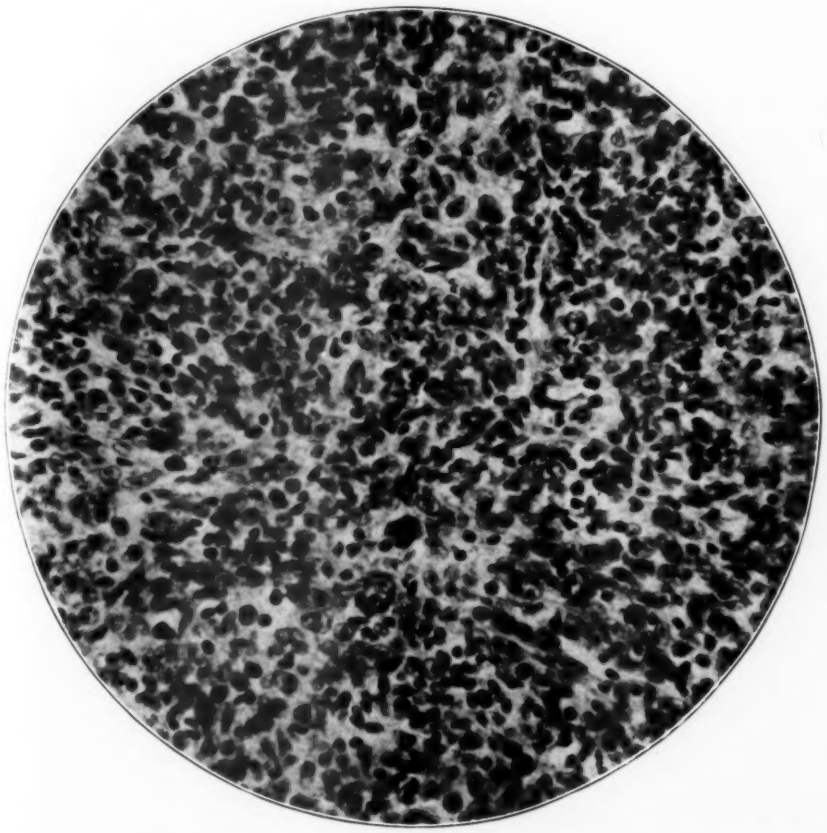

Fig. 14.—Carcinoma of the nasopharynx in a man, aged 25; symptoms: fixation of jaw, enlarged glands of neck, involvement of trigeminus, hemorrhages from mouth and nose; temporary decrease in size of growth and relief of pain after irradiation.

CASE 38.—*History.*—A white man, aged 25, was admitted in February, 1918, complaining of deafness in the right ear, suppurative otitis media on both sides, sore throat for six months, inability to open mouth, enlargement of the glands of the neck on both sides, which were hard and firmly fixed, involvement of the fifth nerve and pain.

Examination.—The Wassermann reaction was negative. There was no difficulty experienced in breathing through the nose. The growth bled easily when touched; there were no spontaneous hemorrhages. When first seen, the growth involved the anterior wall of the sphenoidal sinuses, the posterior part of the septum and the entire region of the orifice of the right eustachian tube.

Diagnosis.—The microscopic diagnosis of a piece of tissue removed from the nasopharynx was carcinoma (Fig. 14).

Treatment.—From Feb. 9, 1918, to Aug. 8, 1919, the patient received intensive radium treatment, consisting of 89,200 mc. hours of gamma radiation at a distance of from 3 to 5 inches applied externally, as well as 666 mc. hours applied directly to the surface of the growth, and two capillary tubes, each containing 5 mc. of radium emanation, implanted in the growth.

Course.—April, 1918, two months after the radium treatment was begun, the growth in the nasopharynx and the metastatic glands in the neck had decreased to about one-tenth their previous size. The jaw remained fixed, and the patient still suffered pain.

July, 1919, there was no evidence of growth in the nose, throat or nasopharynx. The glands of the neck were slightly larger than they were one year previously. There was no evidence of metastasis elsewhere. The general condition was bad. The patient was cachetic; the jaw was still fixed, and the pain was much reduced.

CASE 39.—*History.*—A white man, aged 57, was admitted in September, 1917, complaining of enlarged glands of the neck on both sides, obstruction and pain in the right ear, a constant salty taste, and inability to open the mouth. The first symptom had occurred two months previously.

Examination.—The Wassermann reaction was negative. The growth had originated under the mucous membrane on the right side of the nasopharynx. There was involvement of the fifth nerve.

Diagnosis.—The microscopic diagnosis, made from a specimen of the gland of the neck removed for diagnosis, was squamous-cell carcinoma.

Treatment.—The patient received intensive external irradiation from Oct. 31, 1917, to April 1, 1918, a total of 58,900 mc. hours being given at a distance of from 2 to 4 inches over the right side of the face and the cervical glands.

Course.—The patient died in September, 1918, of cachexia.

CASE 40.—*History.*—A white man, aged 42, was admitted, Feb. 24, 1913, complaining of pain and impairment of hearing in both ears; suppurative otitis media in the left ear, of ten months' duration; enlarged glands of the neck; headaches; hemorrhages from the mouth and nose; diplopia; loss of the sense of smell and taste, and metastases under the zygoma on the left. The onset of symptoms had occurred eighteen months before admission.

Examination.—The Wassermann reaction was negative. There was no involvement of the nose. The growth occupied the entire nasopharynx. There was an ulcerated area near the orifice of the eustachian tube on the left.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—The gland of the neck was removed for microscopic diagnosis. No radium treatment was employed. Treatment was given with Coley's fluid for five weeks in New York by Dr. Coley, with transient decrease in size of the metastatic gland.

Course.—April, 1913, the general condition was much worse. The patient was having severe headaches and attacks of nosebleed. He died May 26, 1913.

CASE 41.—*History.*—A colored boy, aged 11, was admitted in November, 1919, complaining of sore throat, headaches and night sweats until October, 1918, when the tonsils and adenoids were removed. Swelling occurred on the right side of the neck shortly after this. Headache and pain in the neck increased, and the jaw became fixed. The symptoms had been present for seventeen months. The growth possibly originated following the removal of the adenoids and tonsils.

Examination.—The Wassermann reaction was negative. There were enlarged, hard glands in the neck on both sides.

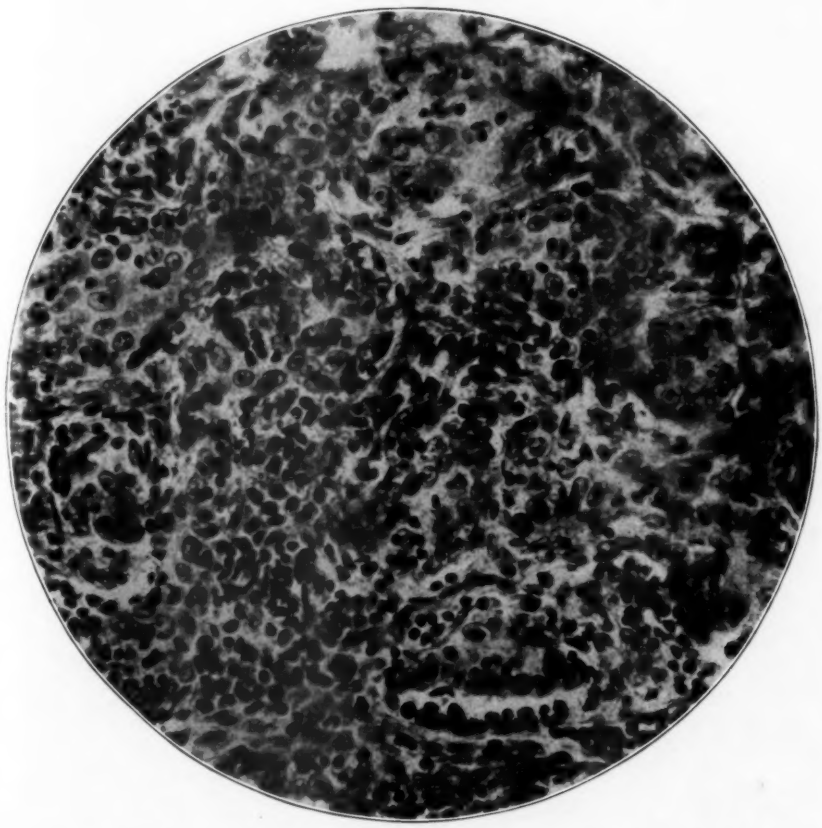

Fig. 15.—Primary carcinoma of nasopharynx with metastatic glands of neck in a boy, aged 11 years, not treated.

Diagnosis.—The microscopic diagnosis made from a piece of tumor removed from the nasopharynx and also from a gland removed for diagnosis was carcinoma.

Treatment.—No radium treatment was given in this case on account of the extensive involvement. Operation was not advised and the patient was discharged untreated.

Course.—There was no subsequent note.

CASE 42.—*History.*—A white man, aged 50, was admitted in October, 1914, complaining of an obstruction in the eustachian tube on the left, following a cold. He had had a blood stained sputum since the onset and severe pain in the left side of the head. There was paresis of the soft palate on the left but no metastasis to the glands of the neck. He had diplopia. These symptoms had begun nine months previously.

Examination.—The Wassermann reaction was negative. The onset of the ear symptoms followed a cold. The ear had been treated by inflation, and later the nasal septum had been straightened. The growth in the nasopharynx was not recognized for nine months, although the patient had a bloody discharge from the onset. On admission there was intracranial involvement; but there were no metastatic glands of the neck and no fixation of the jaw.

Diagnosis.—Tissue removed from the nasopharynx for microscopic examination revealed carcinoma.

Treatment.—The patient was first seen here, Oct. 12, 1914, and was given very little irradiation on that day. Dec. 12, 1914, he was given 5,733 mc. hours of gamma radiation at a distance of 2 inches directed on the left side of the face and neck. The treatment in this case was given only with the idea of palliating pain and was not intensive enough to effect any real change in the growth, as we felt that the disease was so extensive that treatment was useless.

Course.—The patient died one month after the onset of the ear symptoms, with orbital and intracranial involvement.

CASE 43.—*History.*—A white man, aged 31, was admitted in September, 1917, complaining of exophthalmos on the right, and an obstruction of the right side of the nose, with bleeding, the onset of which had occurred four months previously. There were large, hard, firmly fixed glands in the neck on the right.

Examination.—The Wassermann reaction was negative. The point of origin was probably in the posterior part of the nose, the orbit being involved at an early stage.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—The patient was treated from Sept. 16, 1917, to Nov. 25, 1917. During this time, he received several mild treatments; but the total was only 8,100 mc. hours of gamma radiation employed at a distance of 3 inches.

Course.—The patient died ten months after the onset. There was an orbital involvement on the right, with loss of vision, and also terminal intracranial involvement. This patient received local treatment for nasal obstruction for four months before coming to the Johns Hopkins Dispensary.

CASE 44.—*History.*—A white man, aged 54, was admitted in June, 1920. His earliest complaint had been a nasal obstruction on the right, and an obstruction of the right eustachian tube, with bleeding, three years previously. He had had a nasal operation two years previously, and a large amount of tissue was said to have been removed, followed by profuse bleeding.

Examination.—The Wassermann reaction was negative. The growth involved the right side of the nasopharynx and the right nostril. No metastatic glands of the neck were found and no infection of the ears. There had been a history of difficulty in breathing through the nose for seven years.

Diagnosis.—Tissue removed from the nose for microscopic examination revealed carcinoma.

Treatment.—The patient received three radium treatments, June 19, June 23, and June 28, 1920, at a distance of 3 inches, centered over the right and left

sides of the face, a total of 21,200 mc. hours of gamma radiation being employed. There was no improvement after these treatments, and, when the patient was seen, Sept. 3, 1920, the growth had increased, and both nostrils and the nasopharynx were blocked with the growth. He was having severe pain in the back of the head. No further treatment was given.

Fig. 16.—Carcinoma of right nostril and nasopharynx in a man, aged 54; no improvement of any kind following radium treatment.

Course.—In December, 1920, the patient wrote that he was having repeated hemorrhages from the nose and throat, and that the glands of the neck were rapidly increasing in size.

CASE 45.—*History.*—A colored boy, aged 19, was admitted in May, 1915. His earliest symptom had been sore throat and an enlarged gland in the neck, with pain in the right side of the face and eye, for two months. He had had

hemorrhages from the nose and an impairment of hearing on the right. Fixation of the jaw appeared after the onset.

Examination.—The Wassermann reaction was negative. There were hard movable glands on both sides of the neck, with a slight enlargement of the glands of the axillae and groins. The spleen was not enlarged. A roentgenogram of the lungs was negative. The differential blood count was normal; white blood cells, 13,700; hemoglobin, 87 per cent. He had lost 45 pounds during the past two months. There was no elevation of temperature.

Diagnosis.—The microscopic diagnosis was carcinoma, probably arising from the basal layer of the ciliated epithelium in the nasopharynx.

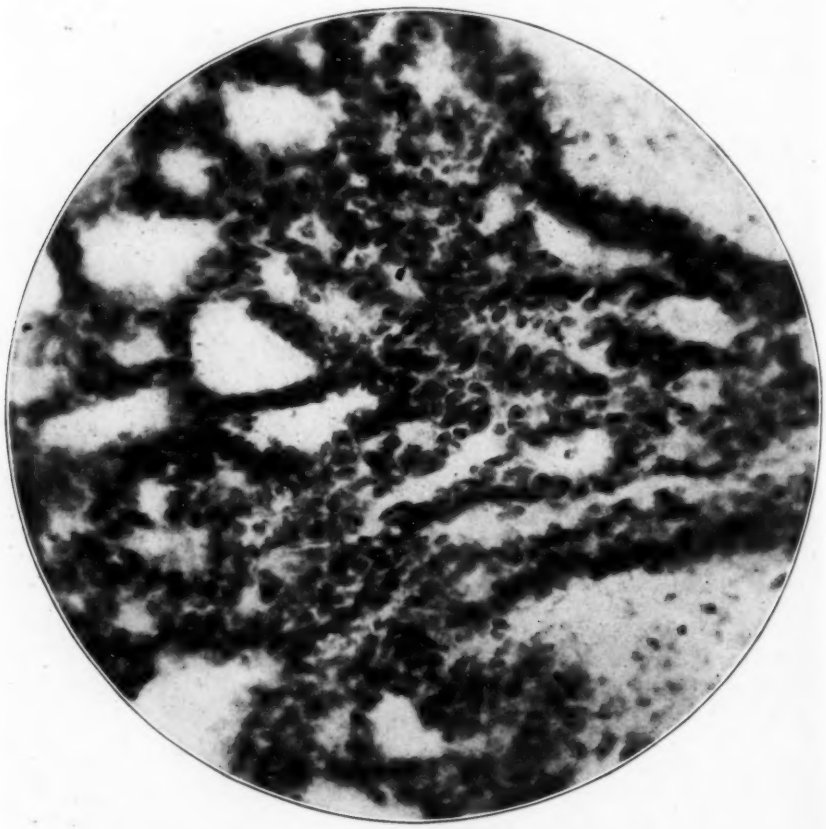

Fig. 17.—A higher magnification of Figure 16.

Treatment.—The patient received two heavy radium treatments: (1) Aug. 3, 1915, 24,900 mc. hours of gamma radiation was employed at a distance of 3 inches, distributed over the right and left cheeks and over the right and left sides of the neck. (2) Oct. 14, 1915, the treatment was employed directly on the tumor in the nasopharynx for one and one-half hours, with 100 mg. of radium bromid—screened with 2 mm. of brass and a thin layer of rubber. Nov. 14, 1915, he received 3,500 mc. hours of gamma radiation at a distance of 1 inch directed over the enlarged glands on the right side of the neck.

Course.—This patient died soon after leaving the hospital. No necropsy was performed.

CASE 46.—*History.*—A colored girl, aged 11, was admitted in November, 1919. Pain and discharge from the right ear had been the first and the only symptoms for one month. There had been stiffness of the jaw and bleeding from the nose and mouth during the previous five months.

Fig. 18.—Carcinoma of the nasopharynx in a girl, aged 11 years; not treated.

Examination.—The Wassermann reaction was negative. She was unable to separate the teeth more than 1 cm. and could take only liquid food. A hard irregular tumor was found in the nasopharynx, occluding the right eustachian tube. It bled easily when touched with a probe. The hemoglobin was 37 per

cent. She was given a transfusion. The glands were enlarged at the angles of the jaws on both sides, but not elsewhere in the body. The nose appeared normal. A roentgenogram of the chest was negative.

Diagnosis.—A piece of tissue removed from the nasopharynx for microscopic diagnosis revealed carcinoma (Fig. 18).

Treatment.—The growth in this case was too advanced for operation, or irradiation. One glass capillary point, containing 4½ mc. of radium emanation,

Fig. 19.—Large metastatic glands in neck. The only symptom of the primary carcinoma in the nasopharynx was bleeding from the mouth; excision of the larger glands and implantation of radium in the smaller ones resulted in an apparent cure for eighteen months; death due to recurrence in mediastinum and esophagus.

was implanted directly into the growth, followed by a very severe hemorrhage four days later.

Course.—There was no report; but the child probably died very soon after leaving the hospital.

CASE 47.—*History.*—A white man, aged 42, was admitted in February, 1913. There had been a history of acute sinusitis, two or three times a year, for the past eight or ten years. The first symptoms had been pain, deafness, a dis-

Fig. 20.—Myxosarcoma involving both sides of nose, nasopharynx and right antrum; no improvement after radium treatment; microscopic appearance shown in Figures 11 and 12.

Fig. 21.—Spindle-cell sarcoma in a child, aged 4 years; first fourteen radium treatments caused the growth to disappear macroscopically, but had no effect on the recurrence.

charge from the left ear, ten months previously. He had had a headache on the left side for ten months, and enlarged glands of the posterior triangle on the left for eight months, with a loss of 40 pounds in weight.

Examination.—The Wassermann reaction was negative. This case was diagnosed as syphilis, and for six months the patient had had mercury and iodids with no benefit. A piece of tumor in the nasopharynx had been removed for diagnosis, six weeks previously. Since that time, hemorrhages had been frequent. He had a low-grade choked disk, paralysis of the sixth nerve on the left, involvement of the second and the third divisions of the fifth nerve on the left. There was palsy of the soft palate on the left.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—The patient was referred to Dr. Coley in New York, who treated him with Coley's fluid for five weeks. The glands of the neck decreased in size; but the general condition became worse. He then went to St. Louis and received injections of colloidal copper, administered by Dr. Loeb, with no benefit. No radium treatment was given in this case.

Course.—The patient died in May, 1913, about one year after the onset of the ear symptom.

CASE 48.—*History.*—A white woman, aged 55, was admitted in April, 1912. The first symptom had been pain in the left side of the head, which had been constant for seven months. There had been pain in the left ear and deafness for six months, but no discharge. She had not complained of nasal obstruction.

Examination.—The Wassermann reaction was negative. There were no metastases to the glands of the neck. She had had cerebrospinal rhinorrhea for four months. A low-grade choked disk was demonstrated, but no involvement of the orbit or the trigeminus. She had palsy of the soft palate on the left. The growth occupied the entire nasopharynx and the posterior half of the nose on the left.

Diagnosis.—No tissue was removed because of the cerebrospinal leakage through the nose.

Treatment.—No treatment was advised on account of the intracranial involvement.

Course.—There was no report; but the patient probably died soon after leaving the hospital.

CASE 49.—*History.*—A colored man, aged 29, was admitted in April, 1911. His first symptom had been pain in the throat, which for three months was ascribed to bad teeth. There had been enlarged glands near the angle of the jaw on the right, which had been noticed four months previously. He had not complained of nasal obstruction, and he had been unable to open the mouth for two months.

Examination.—The Wassermann reaction was negative. Metastatic glands of the neck appeared first on the right, and then on the left. He had a fixation of the jaw. There were large mucous polyps in the right side of the nose, which bled profusely when removed. There was no intracranial involvement. The differential blood count was normal. The growth had apparently originated in the nasopharynx and the posterior naris on the right.

Diagnosis.—The microscopic diagnosis was carcinoma.

Treatment.—The growth in this case was too far advanced for operation or irradiation.

Course.—The patient died, Aug. 8, 1911, at Mercy Hospital, Philadelphia, a little less than a year after onset of the first symptom.

STUDIES IN EXHAUSTION: IV. PHYSICAL TRAUMA

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As stated in the first of these reports,[1] these studies in exhaustion were initiated by an investigation of the cause of surgical shock. Chronologically, therefore, the publication of this article should have preceded that of the studies on insomnia, exertion and emotion.[2] It seemed a more logical sequence, however, to offer evidence of the conditions demonstrated in exhaustion or shock due to extreme degrees of intensity of the factors of normal consciousness before considering exhaustion due to pathologic conditions.

Perhaps no other subject in surgical literature presents so extensive a bibliography as "surgical shock;" but the space at my disposal for this report prohibits any adequate review of this literature, or discussion of the various theories of the causation of shock, such as I have offered in previous publications.[3]

These studies, like those of many other investigators, were undertaken to investigate the essential nature and causation of shock produced by physical trauma. These studies, which are still in progress and have embraced studies of exhaustion due to many different causes, have included observations of the variations in blood pressure produced by physical injury of various organs and tissues; histologic studies of various organs and tissues of animals in shock due to physical injury; investigations of the hydrogen-ion concentration of the blood; estimations of the alkali reserve; measurements of the electrical conductivity of various organs and tissues, and the direct measurement of variations in the temperature of the brain and the liver.

By these various methods, both the immediate and the late effects of physical injury have been studied. Complete reports of some of these researches and summaries of others have been given in previous publications. It is my purpose here to bring together the findings in these studies to the present time, in order that they may be properly recorded and correlated.

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1. Crile, G. W.: Studies in Exhaustion: An Experimental Research, I. Insomnia, Arch. Surg. **2**:196-220 (March) 1921.

2. Crile, G. W.: Studies in Exhaustion: II. Exertion, Arch. Surg. **3**: 116-131 (July) 1921; Studies in Exhaustion: III. Emotion, ibid. **4**:130-153 (Jan.) 1922.

3. Crile, G. W.: Reference Handbook of Medical Sciences **7**:728-734, 1917; A Physical Interpretation of Shock, Exhaustion and Restoration, New York, Oxford University Press, 1921; Mechanism of Shock and Exhaustion, J. A. M. A. **76**:149-155, 1921.

A. BLOOD PRESSURE CHANGES PRODUCED BY PHYSICAL TRAUMA

Since the experimental details of these studies have been presented in detail elsewhere,[4] and a complete summary has been made in a recently published volume,[5] I shall include here only the following general conclusions drawn from these initial studies:

1. There is a quantitative relationship between physical trauma and shock which may be estimated by blood pressure variations; that is, the degree of shock (exhaustion) varies directly with the amount of tissue

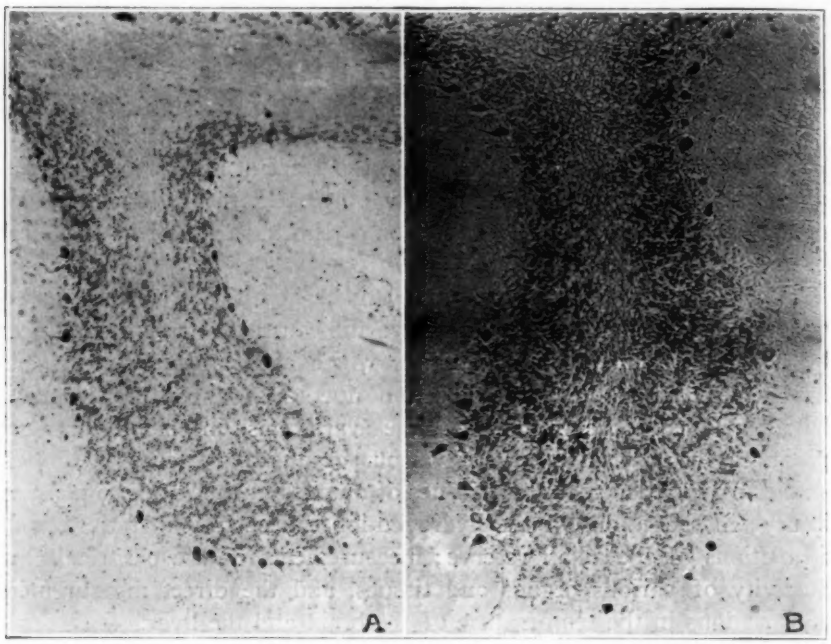


Fig. 1.—Incipient effect of physical trauma upon the brain cells: *A*, section of cerebellum of a normal dog; *B*, section of cerebellum of a dog after severe abdominal trauma for five minutes (reduced from photomicrographs, × 120). The hyperchromatism of the Purkinje cells in *B* may be noted.

injured, with the intensity of the injuring stimulus, with the number of the injuring impacts.

2. The degree of shock produced by physical trauma bears an inverse relation to the phylogenetic protection of the injured tissues; that is,

4. Crile, G. W.: Surgical Shock,1897; Certain Problems Relating to Surgical Operations, 1901; Blood Pressure in Surgery, 1903.

5. Crile, G. W.: A Physical Interpretation of Shock, Exhaustion and Restoration, Footnote 3, pp. 6-40.

the injury of tissues and organs which have been protected throughout the evolution of the organism, e. g., the brain, the lungs, etc., produces but little shock as compared with injury of such exposed regions as the abdomen, the skin and the extremities. Injury of the deep, protected tissues produces collapse rather than shock.

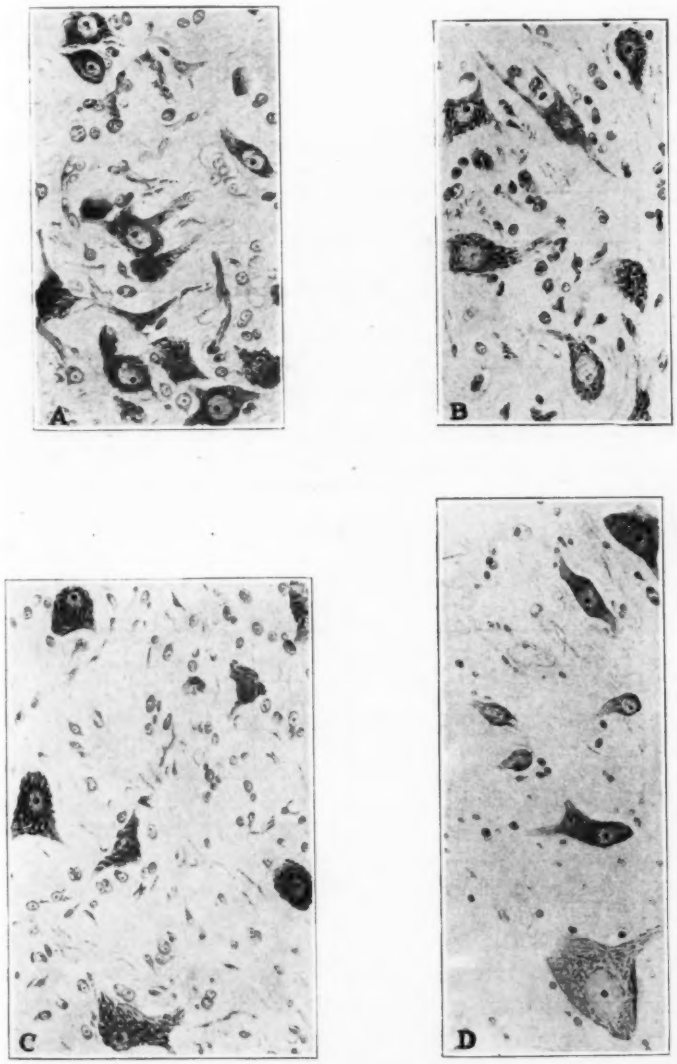


Fig. 2.—Effect of physical trauma on the medulla and the spinal cord: *A*, section of normal medulla; *B*, section of medulla after physical trauma; *C*, section of anterior horn of normal spinal cord in cervical region; *D*, section of anterior horn of spinal cord in cervical region after physical trauma (from camera lucida drawings).

3. The degree of shock bears a direct relation to the nerve supply of the injured tissue.

4. Exhaustion of the vasomotor mechanism is present in shock but is not the only factor in its production.

5. Shock from injury of any tissue can be prevented by blocking the nerve supply of that tissue by a local anesthetic.

B. THE EFFECT OF PHYSICAL TRAUMA ON THE CONSTITUENTS OF THE BLOOD

In collaboration with Drs. F. W. Hitchings, C. H. Lenhart and A. B. Eisenbrey, a series of experiments were performed to determine whether

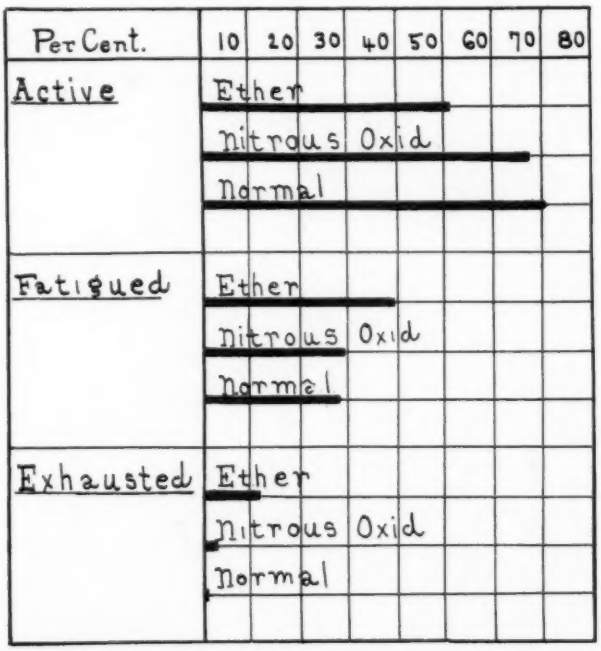


Fig. 3.—Comparison of the effect on the brain cells of abdominal trauma under ether anesthesia with that of like trauma under nitrous oxid anesthesia (differential Purkinje cell counts).

or not the number of red or of white corpuscles or the amount of hemoglobin was affected by physical trauma.

After a preliminary examination of the blood, each dog was subjected to severe intestinal manipulations, and blood examinations were made at successive intervals of about an hour. The blood was taken from the peripheral circulation, usually from the tip of the nose.

The findings in these experiments (Table 1) demonstrate that, in this limited group at least, abdominal trauma produced no notable

change in the blood, excepting in two instances in which there was a marked decrease in the number of white cells.

C. HISTOLOGIC STUDIES

If the vasomotor center was fatigued in shock, as had been demonstrated by the researches described above, then it seemed reasonable to suppose that other portions of the brain would be fatigued also; and, that, if so, the resultant functional alterations of the brain cells would be accompanied by structural changes.

TABLE 1.—Effect of Abdominal Trauma on the Constituents of the Blood

	Blood Pressure, Mm. Hg	Red Cells	White Cells	Hemoglobin, per Cent.
Dog 1:				
Before trauma	110	7,500,000	8,000	100
After trauma				
Count 1	62	6,400,000	16,000	100
Count 2	60	7,660,000	11,500	98
Dog 2:				
Before trauma	114	8,440,000	23,800	100
After trauma				
Count 1	105	8,304,000	12,400	100
Count 2	92	8,944,000	9,100	100
Count 3	88	8,933,000	8,200	100
Dog 3:				
Before trauma	144	6,184,000	25,000	100
After trauma				
Count 1	91	6,608,000	6,900	100
Count 2	40	6,968,000	6,400	100
Dog 4:				
Before trauma	128	5,920,000	23,600	100
After trauma				
Count 1	92	6,240,000	10,400	100
Count 2	60	5,216,000	14,000	100
Count 3	84	7,200,000	25,000	100

Pursuant to this assumption, in 1900, in collaboration with Dr. D. H. Dolley, histologic studies of the brain after traumatic shock were initiated. These studies were continued in collaboration with Dr. J. B. Austin and Dr. F. W. Hitchings and were extended to include other organs and tissues.

The Effect of Physical Trauma on the Cells of the Central Nervous System

Two major groups of experiments were performed; one in which the animals were under ether anesthesia, and one in which trauma, equal to that employed in the first group, was applied to animals under nitrous oxid anesthesia. Dogs were used throughout this series.

As noted in the first section of these reports,[1] nerve cell changes were found throughout the central nervous system, these changes being most marked in the cortex, less marked in the cerebellum and clearly demonstrable in the medulla and the cord. But since the Purkinje cells most graphically portray the various stages of stimulation and

exhaustion, they were used in making the differential counts, and for illustration. The differential counts given in the accompanying tables were made by Dr. F. W. Hitchings; the description of the cell changes was made by Dr. J. B. Austin. Appreciation is also due to Dr. Hitchings for the collection of the data presented in this section of this report, in which it has seemed best to present a fairly complete description of the groups of experiments which have had the most important influence on our conclusions regarding the essential factor in the production of shock.

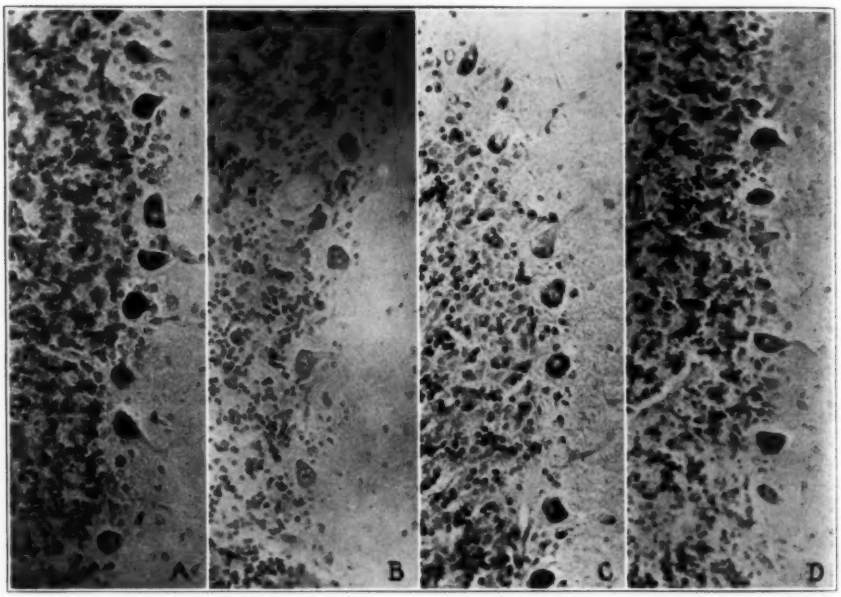


Fig. 4.—Effect on the brain cells of abdominal trauma: *B*, under ether anesthesia; *C*, under nitrous oxid anesthesia; *D*, after severance of the spinal cord at the level of the seventh cervical vertebra: *A*, section of normal cerebellum (reduced from photomicrographs, × 310).

I. Effect of Abdominal Trauma on the Nerve Cells

Group 1. Abdominal Trauma under Ether Anesthesia

Experiment 1.—July 1, 1909: Full ether anesthesia and morphin, ½ grain (0.032 gm.), were used. A dog was reduced to complete surgical shock by means of physical injury without hemorrhage, the blood pressure being taken from the carotid artery in the usual way.

The blood pressure at the beginning of the experiment was 80 mm. After shock-producing manipulations for ninety minutes, the blood pressure was 14 mm. That the dog was in profound shock was evidenced by the fact that no rise in pressure followed the burning of a paw. Sections of the central nervous system were removed, and the dog was killed while still under anesthesia.

Histologic Examination.—The Cerebrum: In the first examination of sections stained by Nissl's method and erythrosin, a few large hyperchromatic pyramidal cells were found. In the extranuclear part of almost all of the other cells, the chromatin was in a state of fine division. The nuclei were not always intact, and many of the nucleoli were disintegrated. These findings were confirmed in two subsequent examinations of freshly cut and stained sections. In a fourth section, the changes seemed even more marked, the large pyramidal cells having a much altered nucleoplasmar relationship. There was marked loss of chromatin; in most of the cells, it had almost disappeared. In some cells, the structure of the nucleus was altered, and the nucleolus was disintegrated. In every case, the findings with the Nissl erythrosin stain were confirmed with borax carmin-hematoxylin.

The Cerebellum: Sections from the cerebellum were examined in detail, and a differential count of 100 Purkinje cells was made (Table 2).

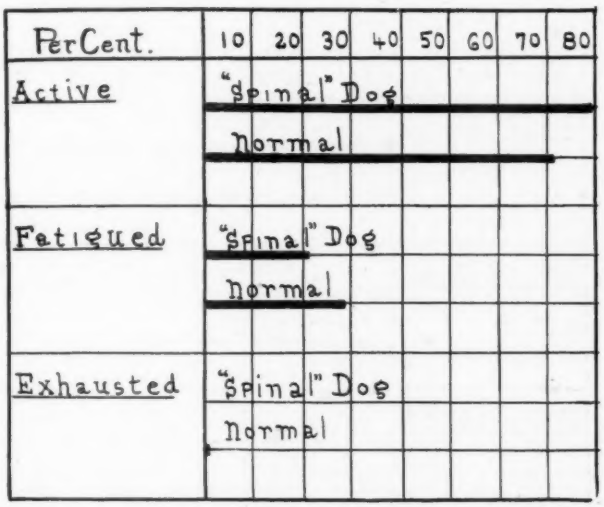


Fig. 5.—Effect on the brain cells of abdominal trauma immediately after the severance of the spinal cord at the level of the seventh cervical vertebra (differential Purkinje cell counts).

The Medulla: The sections from the medulla stained well by both Nissl's method and with borax carmin-hematoxylin. Four of the nuclei of the medulla were present. In three sections, there were very few hyperchromatic cells. In one section, cells in all stages were seen, from the hyperchromatic to those in the exhausted stages.

The Cervical Cord: No hyperchromatic cells were found. Most of the cells had large granules of chromatin; but, in some, the granules were fine and less numerous. In cells from the posterior horn, the nucleoplasmar relationship was disturbed.

Comment.—This was a severely shocked animal, and the brain cell changes corresponded to those produced by physical exhaustion, insomnia, emotion, etc.

EXPERIMENT 2.—July 2, 1909: Ether anesthesia and morphin, ½ grain (0.032 gm.), were used. The blood pressure at the beginning of the experiment was 120 mm.; but it fell almost immediately to 72 mm. After shock-producing manipula-

tions for one hour, the blood pressure was 56 mm., and when a paw was burned the pressure did not rise. Portions of the central nervous system were removed and immediately placed in the fixative solution. The dog was killed while still under anesthesia.

Histologic Examination.—The Cerebrum: An occasional large hyperchromatic pyramidal cell was seen. All the large pyramidal cells showed large, vacuolated nuclei, and absence of, or very finely divided, extranuclear chromatin. The nuclear membrane was always very distinct, and there did not seem to be any exhausted cells. In three other subsequent examinations, the findings were practically the same, excepting that in the last one some exhausted cells with broken-down nuclei were found.

The Cerebellum: A differential count of the Purkinje cells was made (Table 2).

The Medulla: No exhausted cells were found. The chromatin was reduced in quantity and more finely divided than in normal cells. Many cells showed

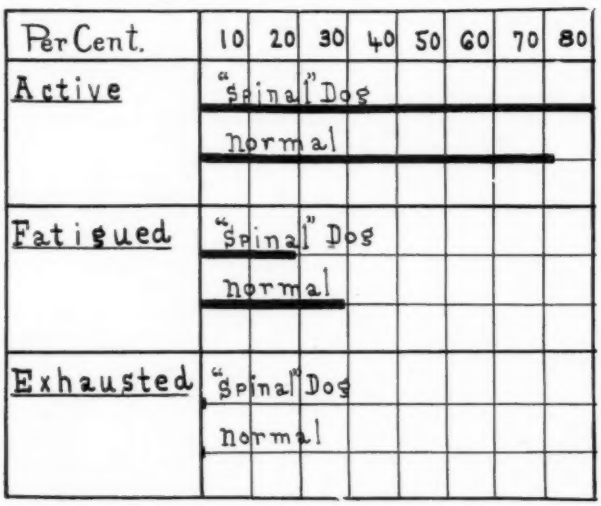


Fig. 6.—Effect on the brain cells of abdominal trauma, two and one-half months after severance of the spinal cord at the level of the seventh cervical vertebra (differential Purkinje cell counts).

enlarged nuclei. Hyperchromatic cells were present, but were not numerous. The sections contained the nuclei of the olive, the accessory olive and portions of the eighth to the twelfth cranial nerves. Findings with both Nissl's stain and borax carmin-hematoxylin were consistent.

The Dorsal Cord: The cells of the anterior horn showed less change than those of Clarke's column. In the former, there were a few hyperchromatic cells, while, in the latter, the chromatin was scanty and finely divided. All the sections stained rather poorly.

Comment.—In this animal, shock was much less severe than in the animal used in Experiment 1, and we found consistently that the cell changes were less marked.

EXPERIMENT 3.—July 17, 1909: Ether anesthesia and morphin, ½ grain, were used. At the beginning of the experiment, after the abdomen was opened, the

blood pressure was 110 mm. After shock-producing manipulations for two and one-quarter hours, the blood pressure was 50 mm. The dog died a few minutes later. Portions of the central nervous system were removed immediately after death.

Histologic Examination.—The Cerebrum: Few of the large pyramidal cells showed hyperchromatism. There were many cells in the first stage of fatigue and many exhausted cells. In some of the latter, the nucleolus was disintegrated, and the entire cell was vacuolated and edematous, or showed a ruptured cell membrane. In making a second examination from newly cut sections, it was found that the various elements were poorly differentiated. When not overstained, the chromatin seemed to be entirely gone.

The Cerebellum: Two differential counts of 100 Purkinje cells each gave the following results:

	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Count 1	31	34	35
Count 2	35	55	10
Normal dog count	71.2	28.1	0.7

The Dorsal Cord: Most of the cells showed absence of, or poorly stained, chromatin. There were no hyperchromatic cells, and only occasionally a cell with large and well-stained granules. All grades of exhausted cells were found, some with the nucleolus completely disintegrated.

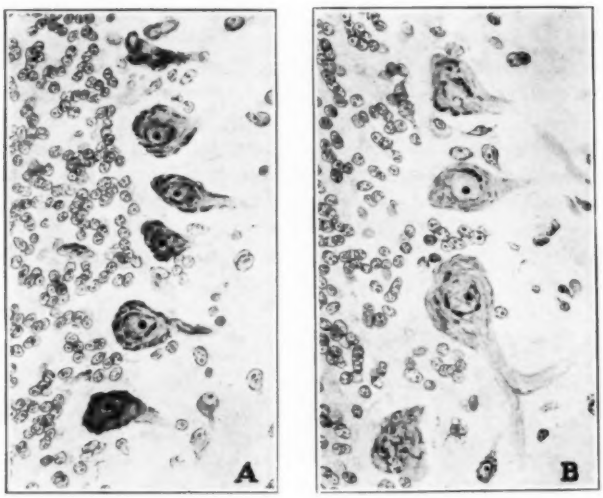
EXPERIMENT 4.—Sept. 19, 1909: Ether anesthesia and morphin, ¼ grain (0.016 gm.), were used. At the beginning of the experiment, before the abdomen was opened, the blood pressure was 120 mm. After shock-producing manipulations of the intestines for three and one-half hours, the blood pressure was 74 mm., and when a paw was burned, the blood pressure rose and the dog showed no symptoms of shock. It was killed after sections of the nervous system had been removed.

Histologic Examination.—The Cerebrum: Only a few hyperchromatic large pyramidal cells were found. The chromatin was in an extremely fine state of division in a large majority of the cells. The nuclei were intact and the nucleoli well stained. Some cells showed a few large chromatin granules, and there were also several exhausted cells. A second examination of new sections only revealed a few hyperchromatic cells. The enlargement of the nuclei was extremely marked, the nucleoplasmar relationship being normal in only a few cells. In some cases, the nucleolus had broken down altogether, while in others it was poorly stained. A third examination revealed the same changes.

The Cerebellum: The differential count of 100 Purkinje cells is given in Table 2.

The Medulla: The larger cells were affected less than the smaller. The nuclei of the cranial nerves and the cells of the reticular formation were almost all hyperchromatic, or, at least, were filled with large granules of chromatin. In the olivary nucleus, there were hardly any hyperchromatic cells. The number of granules was greatly diminished, but still most of the cells had a few scattered granules of good size. No exhausted cells were found, the nucleus in all cases being intact. A second examination confirmed these findings.

The Dorsal Cord: Almost all of the cells were hyperchromatic, the chromatin being in large granules. No fatigued or exhausted cells were found. A second examination confirmed these findings, the granules being large in all but one or two cells.



A B

PerCent.	10	20	30	40	50	60	70	80	90
Active	Shocked Dog.								
	Unshocked Dog.								
	Normal.								
Fatigued	Shocked Dog.								
	Unshocked Dog.								
	Normal.								
Exhausted	Shocked Dog.								
	Unshocked Dog.								
	Normal								

C

Fig. 7.—The comparative effects of abdominal trauma on the brain cells of animals in which the main blood vessels supplying the brains were crossed by anastomosis: *A*, section of cerebellum of untraumatized dog; *B*, section of cerebellum of traumatized dog; *C*, differential Purkinje cell counts (*A* and *B* from camera lucida drawings).

EXPERIMENT 5.—Sept. 30, 1909: Ether anesthesia and morphin, ⅛ grain (0.008 gm.), were used. Before the abdomen was opened the blood pressure was 124 mm., falling to 100 mm. when the manipulations of the intestines were begun. At the end of two hours, the blood pressure was 62 mm., and rose when a paw was burned. The dog was killed, and portions of the central nervous system were removed at once.

Histologic Examination.—The Cerebrum: No hyperchromatic cells were seen, the degree of cell alteration being very marked. Almost all the cells had lost all but a few of their chromatin granules. Many cells were in the last stages of exhaustion, with absence of chromatin, ruptured nucleus, disturbed nucleoplasmar relation and disintegrated nucleolus. At a subsequent examination of a new series of sections, these findings were confirmed, except for the presence of a few hyperchromatic cells, with an assortment of small to large granules in each.

The Cerebellum: Two differential counts of 100 Purkinje cells each were made, which revealed:

	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Count 1	51	41	8
Count 2	62	31	7
Normal dog count	71.2	28.1	0.7

The Medulla: The cells were markedly affected, only a few hyperchromatic cells being seen. Some large cells had large chromatin granules, but most had few granules and showed a disturbed nucleoplasmar relationship, while in all of the sections the small cells showed evidence of fatigue. Some hyperchromatic cells were found; but, in almost all, a great loss and fineness of division of the granules were shown. The cells of the reticular formation were all hyperchromatic.

The Cord: The cells of the anterior horn were mostly hyperchromatic, and contained large granules. In a few cells, the granules were not as numerous but were still larger in size. The small cells were more altered, the granules being fine and the nucleoplasmar relationship disturbed. These findings were confirmed in a second examination.

The Spinal Ganglions: No hyperchromatic cells were seen. In almost all of the cells, the granules were very fine, but the nucleus was intact, and the nucleolus well stained. In each field, from one to four cells were entirely devoid of chromatin. These findings also were confirmed by a subsequent examination.

GROUP 2. ABDOMINAL TRAUMA UNDER NITROUS OXID-OXYGEN ANESTHESIA

EXPERIMENT 6.—May 19, 1909: Nitrous oxid-oxygen anesthesia and morphin were used. At the beginning of the experiment, the blood pressure was 120 mm.; after manipulations for two hours, it had fallen only to 110 mm., and when a paw was burned it immediately rose to 120 mm. There was no clinical evidence of shock at any time. The dog was killed with chloroform, and portions of the central nervous system removed immediately.

Histologic Examination.—The Cerebrum: Most of the cells showed a greatly disturbed nucleoplasmar relationship. There were also many hyperchromatic cells with large granules. Apparently, there were no exhausted cells. A second careful search with high magnification also failed to reveal any exhausted cells.

The Cerebellum: The results of a differential count of 100 Purkinje cells are given in Table 4.

The Cervical Cord: The large motor cells of the anterior horns showed no changes. There were no hyperchromatic cells apparent, but all the cells had large chromatin granules which extended into the dendrites. The cells of the posterior horns showed disturbance of the nucleoplasmar relationship, with diminished chromatin, and in some cases entire absence of chromatin. The nuclei were vacuolated. This condition was in marked contrast to that of the large motor cells, and could not possibly have been due to either fixation or staining.

Experiment 7.—July 9, 1909: Under nitrous oxid-oxygen anesthesia and morphin, the usual shock-producing manipulations of the intestines were made for two and one-half hours, during which time the blood pressure fell from about 120 mm. to 56 mm. As the blood pressure fell to 60 mm. when the

TABLE 2.—The Effects of Abdominal Trauma on the Purkinje Cells of Dogs Under the Influence of Ether-Morphin Anesthesia

	Differential Counts		
Group 1	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Experiment 1	31	42	27
Experiment 2	50	45	5
Experiment 3	33	44.5	22.5
Experiment 4	58	32	10
Experiment 5	56.5	36	7.5
Averages	45.7	39.9	14.4
Normal average	71.2	28.1	0.7

TABLE 3.—Comparison of the Purkinje Cell Counts in Normal and in Traumatized Dogs*

	Differential Counts		
	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Experiment 1:			
Normal dog	73	27	0
Traumatized dog	42	52	6
Experiment 2:			
Normal dog	71	28	1
Traumatized dog	30	55	15

* In each of these experiments, a section from the cerebellum of a normal dog and one from the cerebellum of a traumatized dog were mounted on the same slide and stained and counted by identical technic.

abdomen was opened, it was evident that but a small part of the total fall was due to the subsequent manipulation. At the end of the experiment, there were moderate clinical signs of shock. Portions of the central nervous system were removed intra vitam, and the dog was killed while under anesthesia.

Histologic Examination.—The Cerebrum: The findings in a series of sections with several different fixations and stains were constant. In each were many hyperchromatic cells, chiefly among the large pyramidal cells. The smaller cells showed an almost total loss of extranuclear chromatin, except, usually, a few scattered granules around the periphery. The nuclei were large and unbroken. The nucleoli were usually well stained. There were no exhausted cells. In these cells, there was some disturbance of the nucleoplasmar relation.

The Cerebellum: The results of a differential count of 100 Purkinje cells are given in Table 4.

The Medulla: Most of the cells were small and showed marked fatigue but not exhaustion. They contained very few granules of chromatin; the nuclei were large and vacuolated, and the nucleoli usually well stained. A second series of sections was cut through the nucleus cuneatus and nucleus gracilis. The cells of the remainder of the anterior horn showed the following changes. The motor nuclei around the fourth ventricle showed hyperchromatic cells, and cells with many and larger granules than the foregoing.

The Cord: The block from the spinal cord was cut incorrectly, so that, when the sections were cut from it, only the anterior horn cells showed. These were well stained, had large granules and showed a tendency to hyperchromatism.

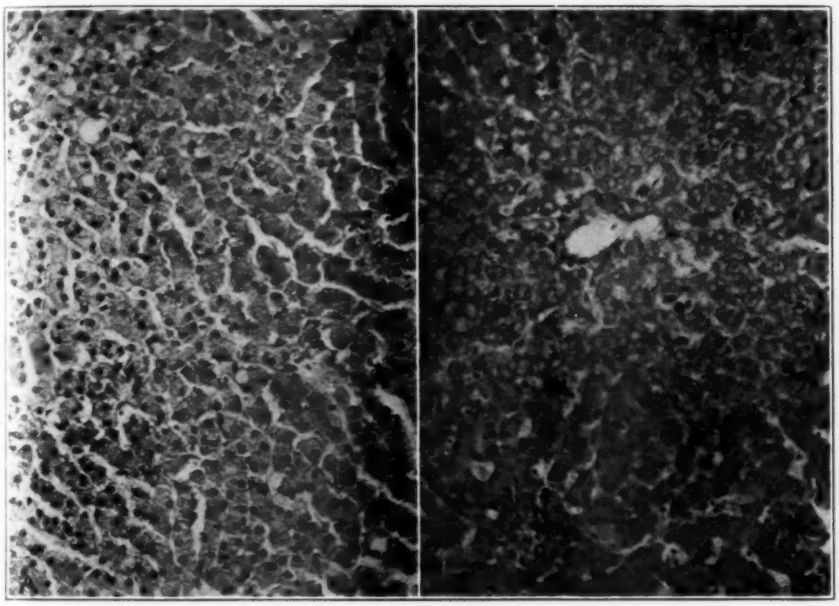


Fig. 8.—Effect of physical trauma on the liver: *A*, section of liver of a normal dog; *B*, section of liver of a dog which had been subjected to severe abdominal trauma (reduced from photomicrographs, × 310).

EXPERIMENT 8.—June 10, 1909: Under nitrous oxid-oxygen anesthesia and morphin, during two hours of intestinal manipulation, the blood pressure fell from 110 mm. to 90 mm. Although the manipulation was severe, no marked symptoms of shock were present at the close of the experiment. Portions of the central nervous system were removed intra vitam, and the animal was killed while under anesthesia.

Histologic Examination.—The Cerebrum: Many of the large pyramidal cells showed changes but no disintegration of the nucleoli. There were many hyperchromatic cells, but most of the cells were in the first stage of fatigue. These findings were confirmed by the examination of a second set of sections.

The Cerebellum: The results of a differential count of 100 Purkinje cells are given in Table 4.

The Medulla: The cells were beautifully stained. Many were hyperchromatic, and all of the rest had large, distinct chromatin granules. The cells of the column of Burdach and those around the points of origin of the cranial nerves, as well as around the fourth ventricle, showed no evidence of fatigue.

The Pons: Most of the cells of the pontine nuclei were hyperchromatic, and none showed loss of chromatin or fatigue changes.

The Cord: The large cells of the anterior horn of the cervical cord showed, in many cases, a loss of chromatin from the dendrites, and a few showed finer granules than those in normal cells and slight evidences of fatigue. In the upper dorsal cord, many cells of the anterior horns had large granules, and many were hyperchromatic. In the smaller and commissural cells, there were smaller and fewer granules. The nucleoplasmar relationship in these cells was altered, the nuclei being very large. The nucleolus was always well stained, and intact.

EXPERIMENT 9.—June 18, 1909: Nitrous oxid-oxygen anesthesia and morphin were used. After the abdomen was opened, the blood pressure was 130 mm. The intestines were manipulated for two hours without hemorrhage, the blood pressure falling to 66 mm. The heart action was strong at this time, and only moderate shock was present. When a paw was burned, the blood pressure rose to 170 mm. The animal was killed while under anesthesia, and portions of the central nervous system were removed immediately after death.

Histologic Examination.—The Cerebrum: In most of the large pyramidal cells, the granules were fine, but, in some, they were absent. The nuclei were intact, and the nucleoli were well stained. The smaller cells (and some of the larger ones) had very large nuclei. A few hyperchromatic cells were found, but some cells were fatigued almost to the point of exhaustion.

The Cerebellum: The results of a differential count of 100 Purkinje cells are given in Table 4.

The Medulla: There were a few hyperchromatic cells, and almost all showed the presence of large granules of chromatin, although in some cells, the granules were few in number and an occasional exhausted cell was found. The level at which all the sections were taken was not determined. In one series of sections from the low medulla, a large number of cells near the point of exit of a motor nerve were in good condition, their granules being large but not numerous. Scattered throughout the fields were many large cells which showed disturbance of the nucleoplasmar relationship and almost complete absence of granules. In some places, the cells were completely exhausted and entirely broken down. There were no hyperchromatic cells.

The Lumbar Cord: The sections were taken at the lumbar enlargement. Almost all the cells contained large and numerous granules of chromatin, and did not seem to be at all fatigued. There were no hyperchromatic cells.

EXPERIMENT 10.—July 5, 1909: Nitrous oxid-oxygen anesthesia and morphin, ½ grain (0.032 gm.), were used. At the beginning of the experiment, the blood pressure was 100 mm., and it did not fall when the abdomen was opened. At the end of three hours of shock-producing manipulation, the blood pressure had fallen to 76 mm., but showed reaction to 84 mm. when a paw was burned. Slight symptoms of shock were present. Portions of the central nervous system were removed intra vitam, and the animal was killed while under anesthesia.

Histologic Examination.—The Cerebrum: Some of the large pyramidal cells were hyperchromatic. Most of the cells were in fair condition, with large masses

of extranuclear chromatin. There was some nuclear vacuolization, but it was not very marked.

The Cerebellum: A differential count of 100 Purkinje cells is given in Table 4.

The Medulla: The sections were taken from a low level. There were marked changes in the cells of the nucleus cuneatus and nucleus gracilis. In most of the cells, there was little chromatin present, and almost all showed disturbance of the nucleoplasmar relation. The cells of the anterior horn were in fairly good condition, many being hyperchromatic.

The Upper Cervical and Dorsal Cord: In most of the cells, the granules were large but scattered, and withdrawn from the dendrites in all except a

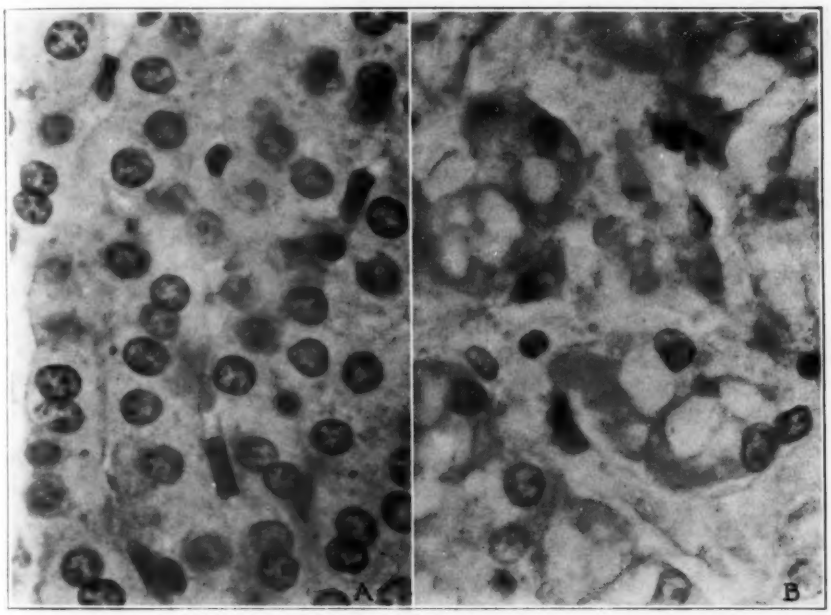


Fig. 9.—Effect of physical trauma on the liver: *A*, section of liver of a normal dog; *B*, section of liver of a dog which had been subjected to severe abdominal trauma (reduced from photomicrographs, × 1,640).

few instances. Most of the cells seemed to be approaching the first stage of fatigue, but there was no disturbance of the nucleoplasmar relation.

EXPERIMENT 11.—June 11, 1909: Nitrous oxid-oxygen anesthesia and morphin were used. After opening the abdomen, the blood pressure was 130 mm. Although the intestines were manipulated for three hours, no symptoms of profound shock appeared, and the blood pressure fell to only 96 mm., rising to 108 mm. when a paw was burned. Portions of the central nervous system, with the exception, through accident, of the cerebellum, were removed intra vitam. The animal was killed while under anesthesia.

Histologic Examination.—The Cerebrum: Many hyperchromatic cells were present, although a majority showed a diminished chromatin content outside the nucleus. The granules were fine. The nuclei were vacuolated, but the

nucleoli were always intact and well stained. On restaining, some cells were found, in each of which the nucleus had a ruptured membrane, and had broken down. Because of these different results, three other examinations were made in which, for the most part, the changes found were those first described.

The Cervical Cord: There were many hyperchromatic cells and others with finely divided or diminished chromatin.

The Dorsal Cord: The same conditions were found, with the granules much less abundant than in normal cells.

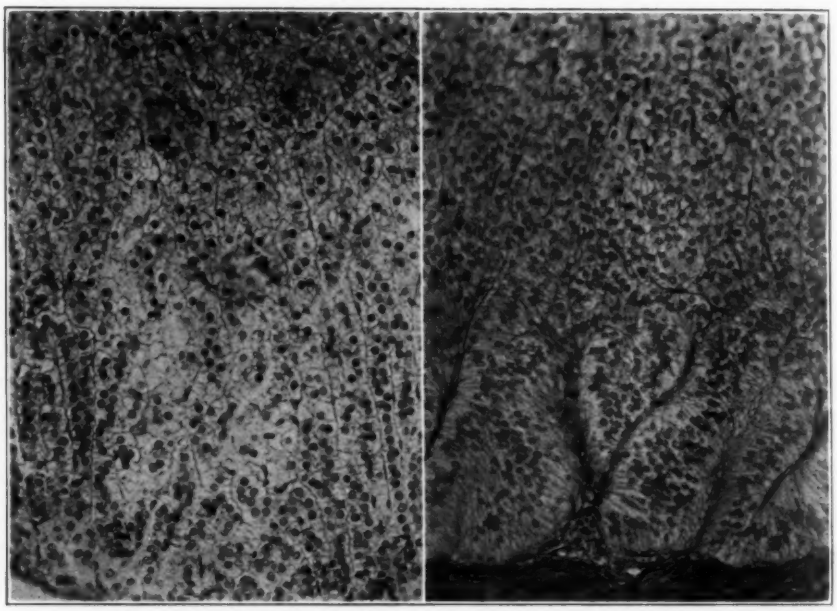


Fig. 10.—Effect of physical trauma on the suprarenals: *A*, section of suprarenal of a normal dog; *B*, section of suprarenal of a dog which had been subject to severe abdominal trauma (reduced from photomicrographs, × 310).

The Spinal Ganglions: The cells of the spinal ganglions attached to the sections from the cord showed variation in the size of the granules, most of which were finely divided. The nuclei were normal.

Experiment 12.—June 3, 1909: Nitrous oxid-oxygen anesthesia and morphin, ½ grain, were used. Before opening the abdomen, the blood pressure was 130 mm. After manipulating the intestines for two hours, the general condition of the dog was good; there were no signs of shock, and the blood pressure had fallen to only 110 mm. Portions of the central nervous system were removed intra vitam, and the dog was killed while under anesthesia.

Histologic Examination.—The Cerebrum: Many of the large pyramidal cells were hyperchromatic. No exhausted cells were found. Most of the cells showed well stained chromatin. The nuclear membrane was unbroken, but usually shrunken. The nucleolus was always well stained. On staining new sections

from the same block, less marked changes than the foregoing were found, there being fewer hyperchromatic cells, with numerous large granules in most of the cells; there were no exhausted cells and no nuclear shrinkage. The findings were the same with Nissl's stain, and with borax carmin-hematoxylin.

The Medulla: Sections were taken at the sensory decussation. The cells of the anterior horn were well stained, the granules being large and numerous. The nucleus cuneatus and nucleus gracilis contained cells which were markedly fatigued, even to the point of exhaustion. The nuclei were vacuolated, as in some cases was the cytoplasm also. The smaller commissural cells also had undergone

TABLE 4.—THE EFFECTS OF ABDOMINAL TRAUMA ON THE PURKINJE CELLS OF DOGS UNDER THE INFLUENCE OF NITROUS OXID-OXYGEN-MORPHIN ANESTHESIA

Group 2	Differential Counts		
	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Experiment 6	83	17	0
Experiment 7	61	33	6
Experiment 8	84	12	4
Experiment 9	57	39	4
Experiment 10	54	41	5
Averages	67.8	28.4	3.6
Normal average	71.2	28.1	0.7

TABLE 5.—EFFECT OF PHYSICAL TRAUMA ON THE PURKINJE CELLS

	Differential Counts		
	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Trauma under ether	45.7	39.9	14.4
Trauma under nitrous-oxid	67.8	28.4	3.8
Normal	71.2	28.1	0.7
Ether anesthesia—four hours*	68.1	27.9	4.0
Nitrous-oxid anesthesia—four hours*	77.0	22.0	1.0

* In order to form a basis for judgment as to what degree the effect of trauma on the brain cells is due to the anesthetic, these figures are appended.

changes resulting in loss of chromatin in the granules and in disturbance of the nucleoplasmar relationship.

The Upper Cervical and Dorsal Cord: Sections from both levels contained cells in good condition. In most instances, the chromatin was well distributed, but showed a tendency to recede from the dendrites. There was also a tendency toward hyperchromatism.

GROUP 3. ABDOMINAL TRAUMA AFTER COMPLETE CROSS-SECTION OF THE SPINAL CORD

The object of these experiments was to determine whether shock-producing afferent impulses from the abdomen could reach and injure the brains of dogs after complete cross-section of the spinal cord between the sixth and seventh cervical vertebrae.

EXPERIMENT 1.—*Abdominal trauma two and one-half months after complete cross-section of the spinal cord.* Sept. 17, 1910: Two and one-half months

before this date, under ether anesthesia, the spinal cord of a dog in good condition was severed between the sixth and seventh cervical vertebrae. The convalescence was stormy, but recovery finally took place, with the exception of complete paralysis below the level at which the section was made, there being a late return of the scratch reflex only. September 17, the dog was anesthetized again with ether and morphin, ½ grain, and subjected to intestinal manipulations. When the experiment started, burning both a front and hind paw did not cause any appreciable rise in blood pressure, although in a normal dog this would have caused a rise of from 10 to 20 mm. at least. After four hours of constant intestinal manipulation the blood pressure had fallen only 8 mm., and burning the paws caused no more reaction than before. At this time, portions of the central nervous system were removed intra vitam, and the dog was killed while under anesthesia.

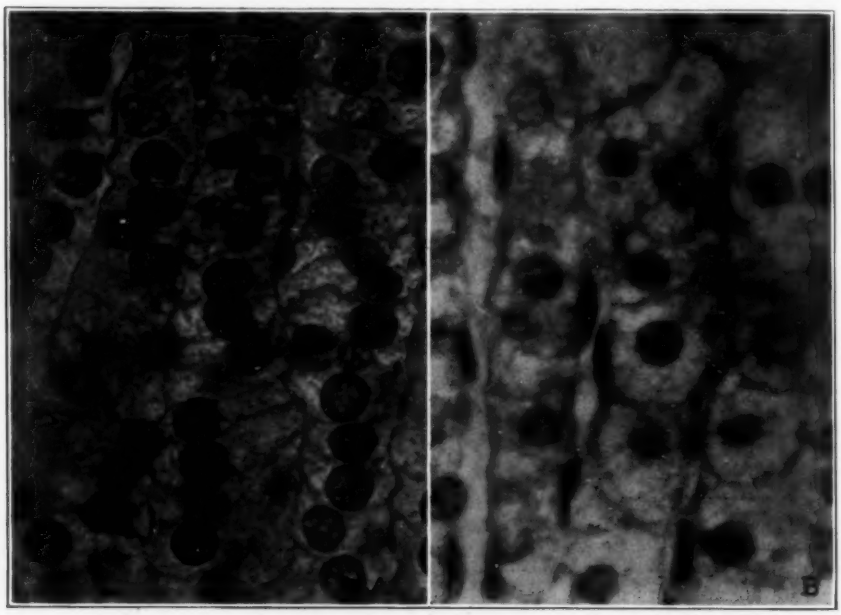


Fig. 11.—Effect of physical trauma on the suprarenals: *A*, section of suprarenal of a normal dog; *B*, section of suprarenal of a dog which had been subjected to severe abdominal trauma (reduced from photomicrographs, × 1,640).

Histologic Examination.—The Cerebrum: The sections were well stained, the cells containing many granules with a normal amount of chromatin. No exhausted cells were found.

The Cerebellum: A differential count of 100 Purkinje cells is given in Table 6.

The Spinal Cord: Above the cross-section, the cells were in normal condition in both the anterior and posterior horns, the granules being large and well stained. At the point of division, the normal tissue had been entirely replaced by connective tissue in bundles.

Below the cross-section, the central canal of the cord was greatly enlarged. The motor cells of the anterior horn were still present. Some were normal in

size and well stained. Others contained finely divided chromatin granules, while an occasional cell was in an exhausted condition. The greatest changes were in the posterior horns. All the cells of Clarke's column and those around the posterior horns showed total loss of chromatin.

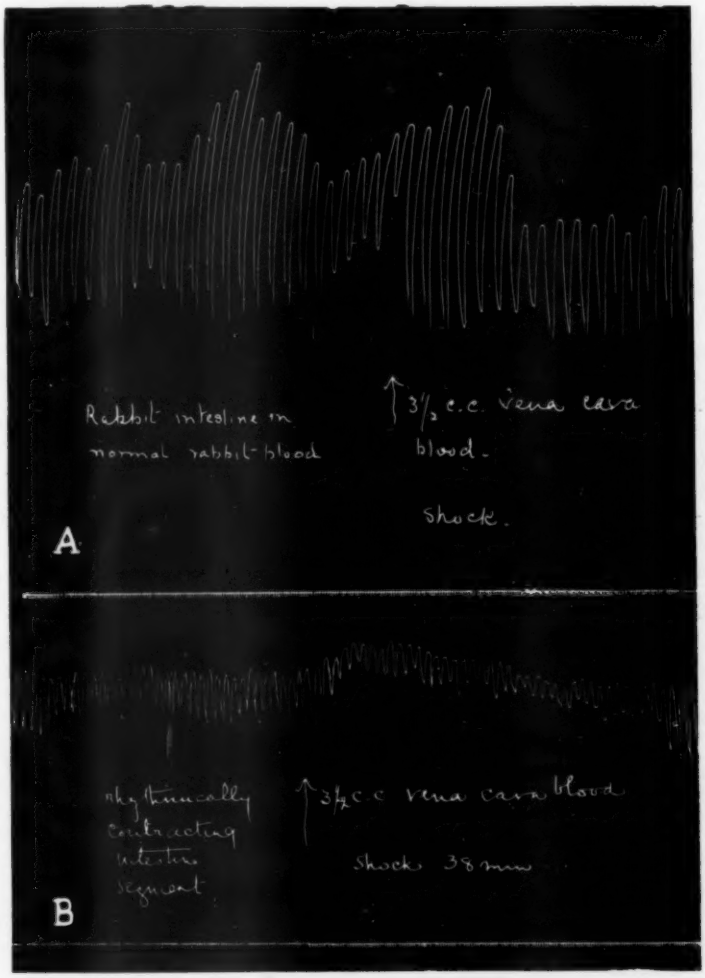


Fig. 12.—Cannon test for epinephrin after abdominal trauma. The lack of reaction when blood from traumatized dogs was substituted for normal blood may be noted. Duration of trauma: Dog A, fifteen minutes; Dog B, thirty-eight minutes.

EXPERIMENT 2.—*Abdominal trauma immediately after complete cross-section of the spinal cord.* Dec. 6, 1911: Ether anesthesia only was used. The spinal cord was severed at the seventh cervical vertebra. There was immediately such a marked fall in blood pressure that it was necessary to transfuse blood from another dog. The abdomen was then opened, and severe shock-producing

manipulations were begun in the usual way. It was found to be impossible to maintain the blood pressure, since blood began to ooze from the liver as soon as the pressure rose. The transfusion was, therefore, made intermittent, only a small amount of blood being allowed to pass at a time. The blood pressure never fell below 30 mm. The animal was killed by stabbing after being subjected to the intestinal manipulations for three hours. The pulse and respiratory rates remained the same throughout the experiment. At necropsy, the complete cross-section of the spinal cord was verified.

Histologic Examination.—The Cerebrum: There was a great preponderance of hyperchromatic cells. In many cells, the granules were not very distinct, the chromatin being somewhat diffused. Very few cells showed any loss of chromatin.

The Cerebellum: A differential count of 100 Purkinje cells is given in Table 6.

EXPERIMENT 3.—*Abdominal trauma immediately after complete cross-section of the spinal cord.* Dec. 7, 1911: Ether anesthesia only was used. The experimental details were the same as in the preceding experiment. One and one-half hours after intestinal manipulations had been begun, the heart suddenly stopped beating as a result of excess of ether. The dog was resuscitated, but it was necessary to administer cardiac massage almost constantly. It was thought that this accident might invalidate the results, but the following data show that it did not. Death occurred at the end of another half hour, or after two hours of manipulations of the intestines.

Histologic Examination.—The Cerebrum: There were many hyperchromatic cells and very few which showed loss of chromatin. The general appearance was normal.

The Cerebellum: A differential count of 100 Purkinje cells is given in Table 6.

EXPERIMENT 4.—*Abdominal trauma immediately after complete cross-section of the spinal cord.* Dec. 14, 1911: Ether anesthesia only was used. The details were the same as in the two preceding experiments. This dog also had to be resuscitated at about the middle of the experiment. The manipulations were continued for three hours, the pulse and respiratory rates being unchanged during that time. As the blood pressure fell, blood was transfused from another dog.

Histologic Examination.—The Cerebellum: A differential count of 100 Purkinje cells is given in Table 6.

COMMENT

This group of experiments indicates that in an animal whose spinal cord has been completely severed no amount of trauma of the distal territories of the body will cause either subjective symptoms of shock or physical changes in the brain cells (Table 6).

GROUP 4. TRANSFUSION OF BLOOD FROM A DOG IN SHOCK TO A NORMAL DOG

In the following experiments the object was to determine whether shock could be transmitted through the blood from a shocked to an unshocked dog. In the first experiments, a dog was subjected to profound shock, and his blood was then transfused to a sound dog.

In two other experiments (the so-called "symbiotic shock" experiments), in each instance, a carotid artery of one dog was anastomosed to a carotid artery of another dog, and an internal jugular vein of one to an internal jugular of the other, the normal directions of current flow being preserved. The blood pressure was taken from the remaining carotid artery of each dog and recorded in the usual way. Ethermorphin anesthesia was used, and each animal was killed before regaining consciousness.

TABLE 6.—Effect on the Purkinje Cells of Trauma After Complete Cross-Section of the Spinal Cord

	Differential Counts		
Group 3	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Experiment 1	80	19	1
Experiment 2	80	19	1
Experiment 3	79	21	0
Experiment 4	89	11	0
Average	82	17.5	0.5
Normal average	71.2	28.1	0.7

TABLE 7.—Comparative Effects on the Purkinje Cells of the Traumatized and of the Untraumatized Dogs in Crossed Circulation Experiments

	Differential Counts					
	Traumatized Dogs			Untraumatized Dogs		
	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Experiment 1	..	..	..	80	20	0
Experiment 2	42	52	6	73	27	0
Experiment 3	30	55	15	71	28	1
Average	36	53.5	10.5	74.6	25	0.3
Normal average	71.2	28.1	0.7			

By this symbiotic arrangement, physiologic continuity of circulation was established, and could be maintained indefinitely. Consequently when one dog of each pair was subjected, for at least three hours, to severe shock-producing manipulations of the intestines it would be expected that if toxic products were formed and liberated into the blood stream, or if shock were due to some alteration in the gaseous content of the blood, they would be transmitted to and affect the brain of the other dog. It would also be expected that it would take a longer time to reduce the manipulated dog to shock, since his blood pressure was maintained, to a certain extent, by the support of the circulation from the normal dog.

The Purkinje cell counts in these three experiments are given in Table 7.

COMMENT

From these experiments, it is apparent that no toxic substances are found in the blood during shock, certainly none of sufficient virulence to have any destructive effect on the brain cells. The tendency toward hyperchromatism is readily explained by the duration of the experiments and the effects of the ether. The important fact is that a negligible percentage of exhausted cells was found and that the clinical symptoms of shock did not appear in the untraumatized dogs.

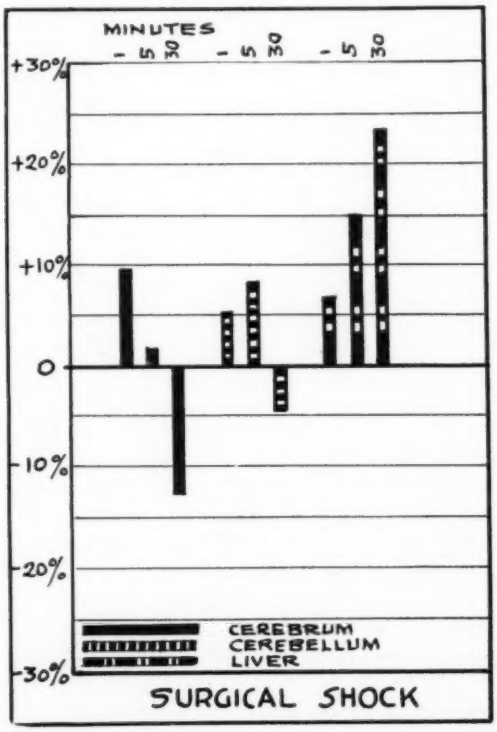


Fig. 13.—Early and late effects of abdominal trauma on the electric conductivity of the brain and the liver.

GROUP 5. MISCELLANEOUS EXPERIMENTS

Under this heading are described five experiments in which there were, accidentally or intentionally, factors which caused variations from the typical experiments described in Groups 1 and 2.

EXPERIMENT 1.—*The effects of abdominal trauma on a dog under interrupted nitrous oxid-oxygen anesthesia and morphin.* The purpose of this experiment was to determine the effect on the brain cells of a bad technic in administering the anesthetic.

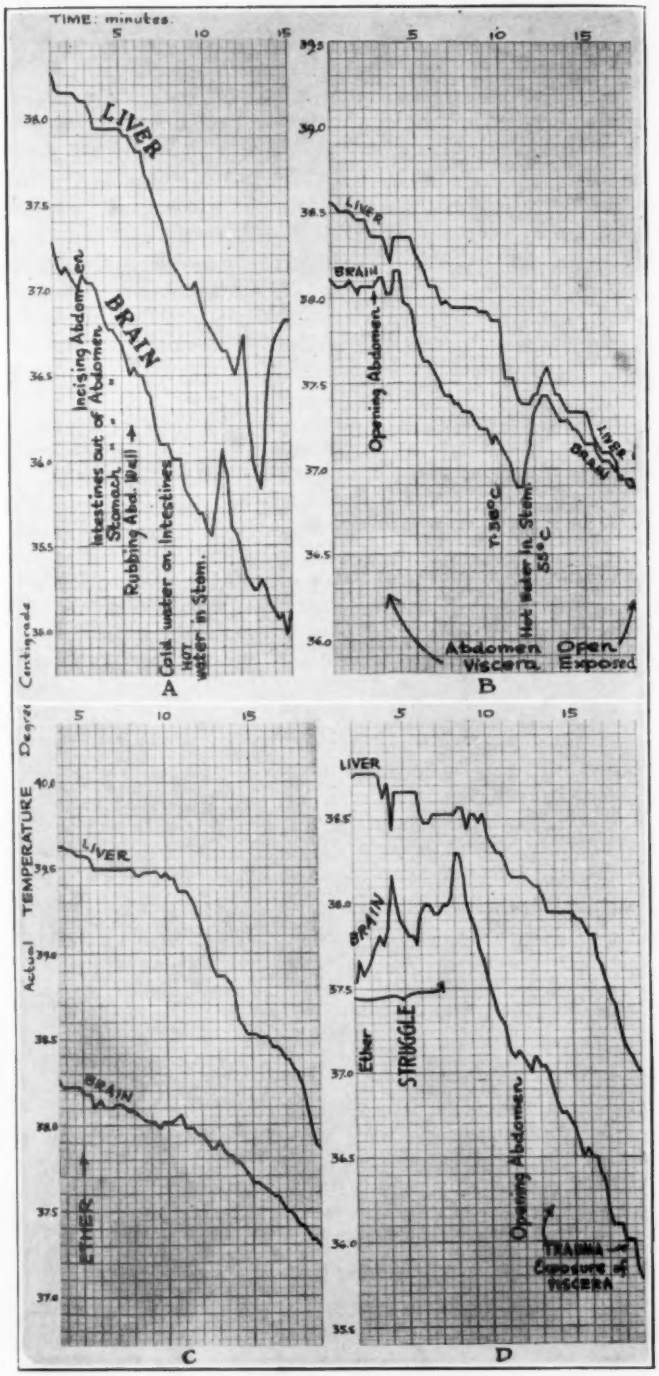


Fig. 14.—Temperature variations in the brain and the liver produced by abdominal trauma (thermocouple measurements). In each of these experiments under ether anesthesia, the abdomen was opened and the intestines and abdominal wall were subjected to shock-producing manipulations. In *C*, the manipulations were more moderate than in the other experiments.

June 8, 1909: Under interrupted nitrous oxid-oxygen anesthesia and morphin, the intestines were manipulated constantly for two hours, during which period the blood pressure fell from 110 mm. to 40 mm., the principal fall occurring when the anesthetic was interrupted. At the end of the experiment, a rise of 10 mm. occurred when a paw was burned. Portions of the central nervous system were removed, and the dog was killed while under anesthesia.

Histologic Examination.—The Cerebrum: There were scarcely any hyperchromatic cells. Most of the cells showed a marked loss of granules, such granules as remained being in a finely divided state. Most of the nuclei were vacuolated, and the nuclei were well stained. The smaller pyramidal cells did not have as large a nucleus as is usual. No markedly exhausted cells were found.

The Cerebellum: A differential count of 100 Purkinje cells was as follows:

	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Count 1	62	34	4
Normal dog count	71.2	28.1	0.7

The Medulla: Most of the motor cells around the fourth ventricle and most of the commissural cells were hyperchromatic. The greatest changes were found in the accessory olive, and those next in degree, in the olive itself. The cells were fatigued but not exhausted, that is, the chromatin granules were diminished in number and size, and the nuclei were enlarged. The cells of the anterior horns were not so hyperchromatic as were the cells of the motor nerves.

The Cord: In the cervical cord, both in the anterior horns and in the commissure, most of the cells contained numerous large separate granules. Many of the cells were hyperchromatic.

EXPERIMENT 2.—*The effects of abdominal trauma under ether-morphin anesthesia on a dog that had distemper and that had fasted five days.* Sept. 29, 1909: Ether anesthesia and morphin, ⅛ grain, were used. The animal had fasted for five days, and had drunk very little water during this time. It coughed and had a discharge from its nose. Before the abdomen was opened, the blood pressure was 110 mm., falling to 78 mm. when the abdomen was opened. The animal was soon in profound shock, and, at the end of one and one-half hours of intestinal manipulation, the pressure had fallen to 34 mm. when the animal almost expired. When a paw was burned, the pressure did not rise. Portions of the central nervous system were removed before death occurred.

Histologic Examination.—The Cerebrum: As a whole, the changes in the nerve cells were very marked. There were no hyperchromatic cells, and only an occasional granule of chromatin was seen in any of the cells, in many of which the nuclear membrane was torn and the nucleolus disintegrated. Sections from another block of cerebral tissue presented the same appearance. Restaining with borax-carmin and iron-hematoxylin gave the same results as the Nissl stain.

The Cerebellum: Two differential counts of 100 Purkinje cells each were as follows:

	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Count 1	52	35	13
Count 2	55	35	10
Normal dog count	71.2	28.1	0.7

These two counts were made from sections taken from two different blocks of cerebellum. The slight variation between them may be noted.

The Medulla: The sections did not pass through the nucleus cuneatus or the nucleus gracilis. The cells of the nuclei around the fourth ventricle

were affected. There were some hyperchromatic cells, and others in which the number of large granules was greatly reduced. The smaller cells showed greater changes, some being entirely without granules. In many cells, both large and small, the nucleus seemed to be enlarged. Sections from another part of the block passed through the nucleus cuneatus and the nucleus gracilis. For the most part, the cells in these nuclei were affected more than were those elsewhere in the section. Very few chromatin granules were present. The nuclei were intact, and the nuclei had stained well. The cells of the formatio reticularis and those around the floor of the fourth ventricle (eleventh or twelfth cranial nerve roots) had larger and more dense granules, and seemed to have been little affected. On restaining with iron-hematoxylin the same changes were found.

The Cord: Moderate changes were found. There were many hyperchromatic cells with large chromatin granules. A few cells had very fine granules, and their dendrites and certain areas in the protoplasm of the cell body were free from chromatin. The nuclear structures were unchanged.

The Spinal Ganglions: There were no hyperchromatic cells or cells with large granules, and, when chromatin was present, it was finely divided. Some cells showed great loss of chromatin. Eccentric nuclei and badly stained nucleoli were present. On staining fresh sections with Nissl's stain, the findings were the same. On restaining with borax carmin and hematoxylin, no hyperchromatic cells were found. The granules were fine for the most part, and some cells had no granules, although in a few the granules were large.

Comment.—The high percentage of exhausted cells is readily accounted for by the fact that, in this experiment, further exhaustion from injury was added to exhaustion from disease and fasting.

EXPERIMENT 3.—*The effects of abdominal trauma on a dog under nitrous oxid-oxygen anesthesia and scopolamin (hyoscin).* The object of this and the following experiment was to determine whether more or less shock would be produced if scopolamin was used instead of morphin.

June 28, 1909: Nitrous oxid anesthesia and scopolamin were used. As soon as the technic for recording the blood pressure was completed, a hypodermic injection of scopolamin, 1/10 grain, was given. Twenty minutes later, the respiration and circulation ceased; but resuscitation was easily accomplished by means of cardiac massage. The abdomen was then opened, and the intestines were manipulated for one and one-half hours, during which period the blood pressure, which was 130 mm. at the beginning of the experiment, fell to 70 mm. Moderate symptoms of shock were present. There was no evidence of marked fatigue or of exhaustion.

Histologic Examination.—The Cerebrum: The largest of the pyramidal cells showed little change in the number and size of the chromatin granules and had apparently been little affected. In some cells, however, the chromatin had disappeared entirely, and the nucleus was vacuolated, while the nucleolus was well stained. In others, small masses of chromatin remained within the nuclear membrane, which in some instances was ruptured. Sections from two other blocks of tissue showed the same changes. The hyperchromatic cells seemed to have more and larger chromatin granules than those in cases in which morphin was used.

The Cerebellum: A differential count of 100 Purkinje cells was as follows:

	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Count 1	79	18	3
Normal dog count	71.2	28.1	0.7

The Medulla: Hyperchromatic cells were rare. Almost all of the cells had large, sharply stained granules; but, in a few, the granules were fine or had disappeared altogether from certain areas in the cytoplasm. In some cells, there was a tendency toward peripheral distribution of the granules.

EXPERIMENT 4.—*The effects of shock on a dog under nitrous oxid-oxygen anesthesia and scopolamin.* June 30, 1909: Nitrous oxid-oxygen anesthesia and scopolamin, 1/10 grain, were used. Before opening the abdomen, the blood pressure was 160 mm.—abnormally high, and it did not fall when the abdomen was opened. At the end of two hours of manipulations, the blood pressure had fallen to 60 mm., and mild symptoms of shock were present. The heart action showed very little irregularity. Portions of the central nervous system were removed intra vitam, and the dog was killed while under anesthesia.

Histologic Examination.—The Cerebrum: In the large pyramidal cells, most of the extranuclear chromatin was lost, and the cell body was much vacuolated. A few cells were hyperchromatic. There were no exhausted cells. On recutting and restaining, the same changes were found, and in addition there were some cells in which the nucleoli were red instead of blue and were placed eccentrically.

The Cerebellum: Two differential counts of 100 Purkinje cells each were as follows:

	Active Cells, per Cent.	Fatigued Cells, per Cent.	Exhausted Cells, per Cent.
Count 1	56	35	9
Count 2	59	36	5
Normal dog count	71.2	28.1	0.7

The Medulla: The sections were from the level of the fifth cranial nerve. Hyperchromatic cells were present. Most of the cells were well stained, and contained fairly large chromatin granules. In some places, especially in the substantia nigra, the granules were fewer in number and smaller in size. Cells of the tegmental nucleus were present, and showed some changes. Very little change was found in the nucleus of the fifth nerve. On recutting and restaining the findings were practically the same, a larger proportion of hyperchromatic cells being found.

The Cord: The sections were well stained. In some cells, the granules were large but scattered, while in others they were fine.

COMMENT

Experiments 3 and 4 present no evidence of any material variation produced by the substitution of scopolamin for morphin, although in Experiment 4 it is difficult to account for the larger percentage of exhausted cells.

GROUP 6. EFFECT OF ABDOMINAL TRAUMA ON OTHER ORGANS THAN THOSE OF THE CENTRAL NERVOUS SYSTEM

In a later series of studies than those described thus far, dogs were subjected to like trauma under varying conditions, and sections were taken of various other tissues than those of the central nervous system. The details of most of the experiments in this group were carried out by Dr. R. E. Mosiman and Dr. W. B. Rogers, and the histologic exam-

inations, as in the former experiments, were made by Dr. Austin. No differential Purkinje cell counts were made.

EXPERIMENT 1.—*Abdominal trauma under ether.* Feb. 2, 1914: Under ether anesthesia, vigorous manipulations of the intestines and lower muscles were carried out for three hours.

Histologic Examination.—Cerebellum: The cells were generally fatigued and exhausted, although there were a few hyperchromatic Purkinje cells.

Suprarenal: The entire cortex and medulla showed great loss of cytoplasm, the cells being irregular, with eccentric nuclei.

Spleen: The lymph spaces were greatly enlarged; the number of nuclei of the cells was apparently decreased.

Testicle: This was normal.

Lymph Gland: The lymph spaces were distended.

EXPERIMENT 2.—*Abdominal trauma under ether.* May 18, 1916: Ether anesthesia was used. Sections of the muscle and liver were taken before the intestinal manipulations were started. Vigorous manipulations of the intestines and peritoneum were carried out for two hours.

Histologic Examination.—Cerebrum: An occasional hyperchromatic and active cell was found. Most of the cells were fatigued; some were exhausted.

Cerebellum: There were many hyperchromatic and active cells; some were fatigued, a few were exhausted.

Liver: The control section showed a slight loss of cytoplasm. The "shock section" showed a greater loss of cytoplasm, and some vacuolation which was greatest around the central vein.

Suprarenal: Great loss of cytoplasm and vacuolation were evident in the outer half of the cortex; there was some loss of cytoplasm in the medulla.

Muscle: Normal and "shock sections" were identical in appearance.

EXPERIMENT 3.—*Abdominal trauma under ether.* Aug. 8, 1916: Under ether anesthesia, intestinal manipulations were performed for three hours.

Histologic Examination.—Cerebrum: No hyperchromatic or active cells were present; nearly all cells were fatigued, some were exhausted.

Cerebellum: An occasional hyperchromatic and active cell was found; most of the cells were badly fatigued, some were exhausted.

Liver: There was slight loss of cytoplasm in some areas.

Suprarenal: Marked loss of cytoplasm and vacuolation were evident in both the cortex and the medulla.

EXPERIMENT 4.—*Abdominal trauma under morphin.* April 14, 1914: Three grains of morphin were given just before the experiment was started. Ether was given during the dissection for exposure of the carotid artery for blood pressure tracing. Intestinal manipulations were performed for two hours and twenty minutes.

Histologic Examination.—Cerebrum: There were numerous hyperchromatic and active cells—many fatigued and some exhausted.

Cerebellum: A few hyperchromatic cells were present: many active, some fatigued, and an occasional exhausted cell.

Medulla: All cells were hyperchromatic with large granules.

Spinal Cord: Motor cells were active, with small granules; there were no hyperchromatic cells.

Suprarenal: There was very slight loss of cytoplasm in the outer cortical cells; the medulla was well stained.

Kidney: The glomeruli, capsule and tubules were normal.

Stomach: This was normal; the mucosa was well stained, and the cells were well differentiated.

Thymus: This was very large and lobulated, with much adenoid tissue; the corpuscles were very small.

Spleen: This was normal and full of lymphocytes.

Lymph Gland: This was normal, well stained, contained many lymphocytes, and there was no congestion.

Submaxillary Gland: This was normal and well stained.

Voluntary Muscle: This was normal; and the striations were faint.

Heart Muscle: This was normal.

Testicle: This was well stained. There was no spermatogenesis nor spermatozoa.

Lung: This was normal.

TABLE 8.—Histologic Findings in Crossed Circulation Experiments 5 and 6, Group 6

Tissue	Dog A—Traumatized	Dog B—Not Traumatized
Cerebrum:		
Experiment 5	No hyperchromatic cells; all fatigued	Some hyperchromatic cells; many fatigued
Experiment 6	No hyperchromatic cells; all fatigued or exhausted	Many hyperchromatic cells; few fatigued
Cerebellum:		
Experiment 5	Few hyperchromatic cells; in worse condition than B	Some hyperchromatic cells; many exhausted
Experiment 6	No hyperchromatic cells; all fatigued or exhausted; distinctly worse than B	Occasional hyperchromatic cells, many fatigued
Liver:		
Experiment 5	Slight uniform loss of cytoplasm	Marked loss of cytoplasm and large vacuoles
Experiment 6	Old fatty degeneration between lobules; cells almost normal	(Section was missing)
Suprarenal:		
Expermient 5	Normal	Normal
Experiment 6	Practically normal	Practically normal

Comment.—In this experiment, the general appearance of the brain cells was far better than in the case of like trauma under ether alone or with the addition of a small amount of morphin.

Experiment 5.—*Abdominal trauma to one of two dogs united by crossed circulation.* Jan. 25, 1917: Under ether anesthesia, reciprocal anastomosis of the carotid arteries and jugular veins was accomplished in the usual way, and the intestines of one of the dogs were traumatized more or less continually for three hours. During this period, the temperature of the traumatized dog fell from 37.4 to 33.7 C. or 3.7 degrees; while the temperature of the untraumatized dog fell only 1.1 degree—from 38.2 to 37.1 C.

The animals died within two or three minutes of each other, and sections of the brain, liver and suprarenals of each were taken immediately.

The comparative histologic findings are given in Table 8.

Experiment 6.—Feb. 1, 1917: The details of this experiment were the same as those of Experiment 5 described above. The comparative histologic findings are given in Table 8.

Comment.—As in the crossed circulation experiments in a previous group, there is a distinctly worse condition in both the cerebrum and cerebellum of the dog subjected to intestinal trauma than in the untraumatized dog.

SUMMARY OF HISTOLOGIC FINDINGS

1. Physical injury causes changes in the cells of the central nervous system (Figs. 1 and 2).

2. The changes in the cells of the cortex and cerebellum are more marked than those in the medulla and cord, and the changes in the medulla are more marked than those in the cord.

3. The extent of the changes in the brain cells are in direct relation to the duration and the intensity of the trauma.

4. The changes in the brain cells produced by traumatism of an animal under ether anesthesia are many times greater than those produced by approximately equal trauma of an animal under nitrous oxid anesthesia (Fig. 3).

5. The brain cell changes produced by traumatism of an animal under ether or nitrous oxid anesthesia are greater than those produced by either anesthetic alone.

6. No brain cell changes are produced by traumatism of the distal areas in a dog whose spinal cord has been completely severed (Figs. 4 to 6).

7. Shock cannot be transmitted through the blood stream (Fig. 7).

8. If a stated blood pressure is maintained by transfusion, brain cell changes will still occur as a result of traumatism.

9. A limited series of experiments indicates that, in addition to the central nervous system, only the liver and, to a slight degree, the suprarenals are histologically altered in shock (Figs. 8 to 11).

10. The evidence from our histologic studies unfailingly supports the assumption that the essential lesions in traumatic shock are in the central nervous system.

D. PHYSICOCHEMICAL AND FUNCTIONAL STUDIES

Studies of the Suprarenal Output

In three animals, tests of the effect of abdominal trauma on the suprarenal output were made in our laboratory by Dr. Hitchings, using Cannon's method. In two instances, no reaction was secured immediately after the application of intense trauma for ten minutes (Fig. 12). In another instance, the intestinal manipulations were continued for one-half hour, at the termination of which, the test for epinephrin was negative. The intestinal manipulations were then continued for fifteen minutes more, the blood again giving no reaction to the test for epinephrin. Blood taken after death was negative also. Ether anesthesia was employed throughout these experiments.

Chemical Content of Certain Tissues

Eight cats were subjected, under ether anesthesia, to intestinal manipulations for thirty minutes, at the termination of which time,

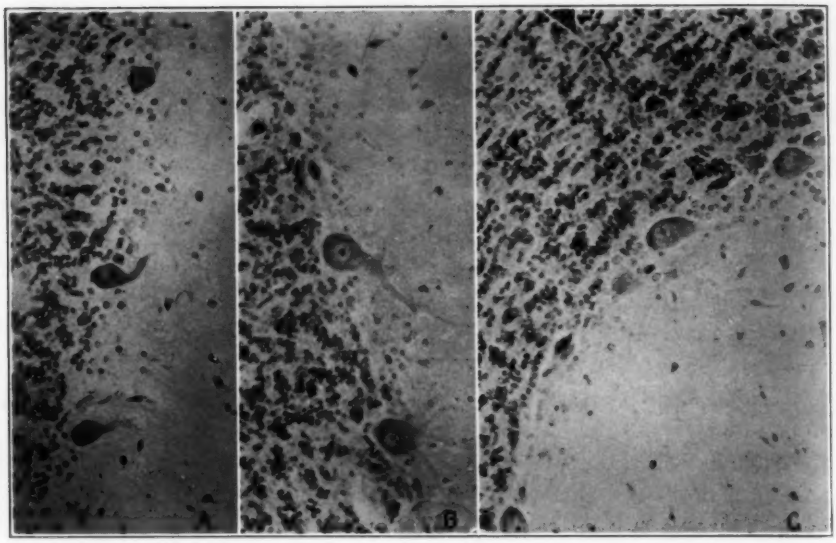


Fig. 15.—Effect of physical trauma on the cerebellum: *A*, section of normal human cerebellum; *B* and *C*, sections of cerebellum of a soldier who died at a casualty clearing station from extensive abdominal wounds (reduced from photomicrographs, × 310).

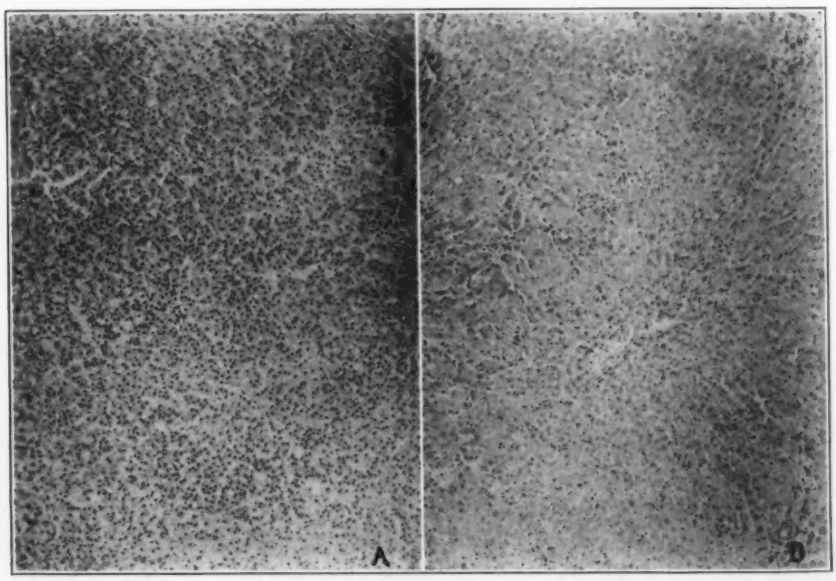


Fig. 16.—Effect of physical trauma on the liver: *A*, section of normal human liver; *B*, section of liver of a soldier who died at a casualty clearing station from extensive abdominal wounds (reduced from photomicrographs, × 120).

the glands and tissues were removed. These, with like glands and tissues from normal cats, were sent to Parke, Davis and Company, where assays were made through the courtesy of Dr. Houghton and Messrs. Briggs, Hamilton and Rowe.

The results of these assays as given in Table 9 demonstrate that, in the traumatized animals as compared with the normal animals (1) the iodin content of the thyroid gland was increased; (2) the epinephrin

TABLE 9.—PHYSIOCHEMICAL STUDIES OF THE EFFECT OF PHYSICAL TRAUMA ON CERTAIN ORGANS AND TISSUES

	Thyroid: Iodin Content, per Cent.	Suprarenals: Epinephrin Content, per Cent.	Suprarenals: Epinephrin Activity, per Cent. of Standard	Liver: Glycogen Content, per Cent.	Muscle: Glycogen Content, per Cent.	Hypophysis: Pituitrin Activity, per Cent. of Standard
Normal cats.....	0.01	0.1	5	0.508	0.56	25
Traumatized cats..	0.03	0.054	2.7	0.056	0.305	20

TABLE 10.—EFFECT OF PHYSICAL TRAUMA ON THE H-ION CONCENTRATION OF THE BLOOD

Experiment 1	Blood from normal dog.....	7.61, 7.61
	Blood taken forty minutes after intestines had been manipulated for one and three-fourths hours (ether anesthesia)....	7.11
	Blood taken seventy minutes after cessation of trauma.....	6.97, 6.99
Experiment 2	Blood from normal dog.....	7.48, 7.44
	Blood taken sixty minutes after intestines had been manipulated for one and three-fourths hours (ether anesthesia)....	7.19, 7.08
Experiment 3	Blood from normal dog.....	7.63, 7.63
	Blood taken thirty minutes after intestinal manipulations started	7.31, 7.27
	Blood taken fifty minutes after intestinal manipulations started	7.24
	(The intestinal manipulations continued throughout period)	

content and epinephrin activity were decreased; (3) the glycogen content of the liver and of voluntary muscle was decreased, and (4) the pituitrin activity was decreased.

MEASUREMENTS OF H-ION CONCENTRATION AND OF RESERVE ALKALINITY

Three studies of the effect of intestinal trauma on the H-ion concentration of the blood made by Dr. M. L. Menten, the results of which are given in Table 10, reveal that, in every instance, the H-ion concentration was markedly increased.

A measurement, made by Dr. W. B. Rogers, of the reserve alkalinity by the Van Slyke method disclosed a diminution in the carbon dioxid combining power from 42 c.c. for each hundred cubic centimeters of plasma to 21 c.c. (vein) and 26 c.c. (artery), after manipulations of the intestines for two hours. With ether anesthesia alone for the same period, the reduction was from 46 c.c. to 32 c.c.

In the laboratory of U. S. Base Hospital No. 4 (The Lakeside Unit) in France, Major A. B. Eisenbrey and Lieut. F. De Eds made comparative studies of the blood from the longitudinal sinus and from the femoral vein, by Martin's titration method.

In these experiments, the preliminary samples of blood were removed under nitrous oxid anesthesia. The anesthetic was then changed to ether, and the animals were subjected to intestinal trauma for one-half hour, when samples of blood were again taken.

TABLE 11.—Comparison of the Reserve Alkalinity of Blood Before and After Intestinal Trauma for One-Half Hour

	Before Trauma		After Trauma (One-Half Hour)	
	Blood from Femoral Vein	Blood from Longitudinal Sinus	Blood from Femoral Vein	Blood from Longitudinal Sinus
Experiment 1.....	0.513	0.445	0.475	0.475
	0.5	0.43	0.47	0.48
Experiment 2.....	0.38	0.3055	0.545	0.385
Experiment 3.....	0.35	0.325	0.46	0.55
	0.35	0.33	0.45	0.54
Experiment 4.....	0.5	0.425	0.525	0.578
	0.5	0.43	0.53	0.58
Experiment 5.....	0.67	0.445	0.61	0.5
	0.675	0.45	0.555	0.45

TABLE 12.—The Effects of Surgical Operation Under Nitrous Oxid Anesthesia Upon the H-ion Concentration of the Blood (Clinical Cases)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Before operation	7.65	7.65	7.53	....	7.63	....
Nitrous oxid analgesia (descending).....	7.60	....	7.41	7.57	7.46	7.55
At end of one hour on operating table...	7.54	7.60	7.26	7.29	7.46	7.50
Nitrous oxid analgesia (ascending).....	....	....	....	7.40	....	7.53
One hour after operation.....	....	7.63	7.42	....	7.53	7.57

The results in five experiments are given in Table 11, which reveals that the blood taken after a half hour of trauma showed a higher alkali reserve in the blood of both the longitudinal sinus and the femoral vein, comparing sinus with sinus, and vein with vein.

In each of the other two cases, the alkali reserve of the blood from the longitudinal sinus was increased, the blood from the femoral vein showing a decrease. In summary, our H-ion and reserve alkalinity studies appear to show an increased alkali reserve in the earlier stages of shock, with a decreased alkali reserve in the later stages.

As a corollary to these experimental determinations may be noted a series of measurements of the H-ion concentration in patients before and after surgical operation under nitrous oxid anesthesia (Table 12).

Electric Conductivity Measurements

Under ether anesthesia, three groups of rabbits were subjected to intense shock-producing manipulations of the intestines for periods of one, of five, and of from thirty to forty-five minutes, respectively. Each animal was killed immediately, and conductivity measurement made of the cerebrum, cerebellum and liver.[6] The average of the measurements of the animals in each group was compared with the average of the measurements of a like number of normal animals which, with the animals subjected to trauma, had been kept for some time under identical conditions in our laboratory. The measurements from the three normals and from the traumatized animals are given in Table 13, and a comparison of the early and late effects of trauma is shown graphically in Figure 13.

TABLE 13.—Comparison of the Early and Late Effects of Physical Trauma on the Electric Conductivity of the Brain and the Liver

Date	Length of Trauma	No. of Animals	Cerebrum	Average Deviation, per Cent.	Percentile Deviation from Normal	No. of Animals	Cerebellum	Average Deviation, per Cent.	Percentile Deviation from Normal	No. of Animals	Liver	Average Deviation, per Cent.	Percentile Deviation from Normal
11-6/18/19	Normal Group VI	8	00172	1.7	.....	8	00131	1.0	.....	6	00101	1.7	.....
6/9/19	Trauma, 1 min.	5	00189	1.0	+ 9.8	6	00138	1.3	+ 5.3	4	00108	1.9	+ 6.9
6/6/19	Trauma, 5 min.	3	00175	0.8	+ 1.7	3	00142	1.9	+ 8.3	3	00116	6.5	+14.8
1/3-2/19/19	Normal Group III	5	00192	1.6	.....	5	00162	5.3	.....	5	00074	2.2	.....
1 8-1/10/19	Trauma, 30-45 min.	5	00168	2.4	—12.5	5	00154	1.7	— 4.9	6	00091	5.5	+22.9

Thermo-Electric Studies of Temperature Variations in the Brain and in the Liver

In order to determine whether or not the variations in the structure and in the electric conductivity of cells, which we have described above, are parts of the same process as that manifested by changes in functional activity, it was necessary to devise some method whereby the functional changes in the cells might be measured in the living animal.

Variations in functional activity indicate variations in oxidation; variations in oxidation are manifested by variations in heat production.

For the accurate measurement of these variations, if present, we devised thermocouples which could be applied directly to the brain, liver or other tissues of the living animal.

6. Crile, G. W.; Hosmer, H. R., and Rowland, A. F.: The Electrical Conductivity of Animal Tissues Under Normal and Pathological Conditions, Am. J. Physiol. **60**:59-106 (March) 1922.

A description of the arrangement of the apparatus for these studies and a review of the literature pertaining to this method of temperature measurement have been published elsewhere.[7] We shall confine ourselves here to a brief statement of our observations of the temperatures in the brains and livers of animals subjected to physical injury.

In most instances, contact with the animal under observation produced an immediate alteration in the temperature of the brain. In the case of severe trauma, produced by shock-producing manipulations of the intestine, a progressive decrease in the temperature of the brain and of the liver was noted. The temperature of the brain usually rose

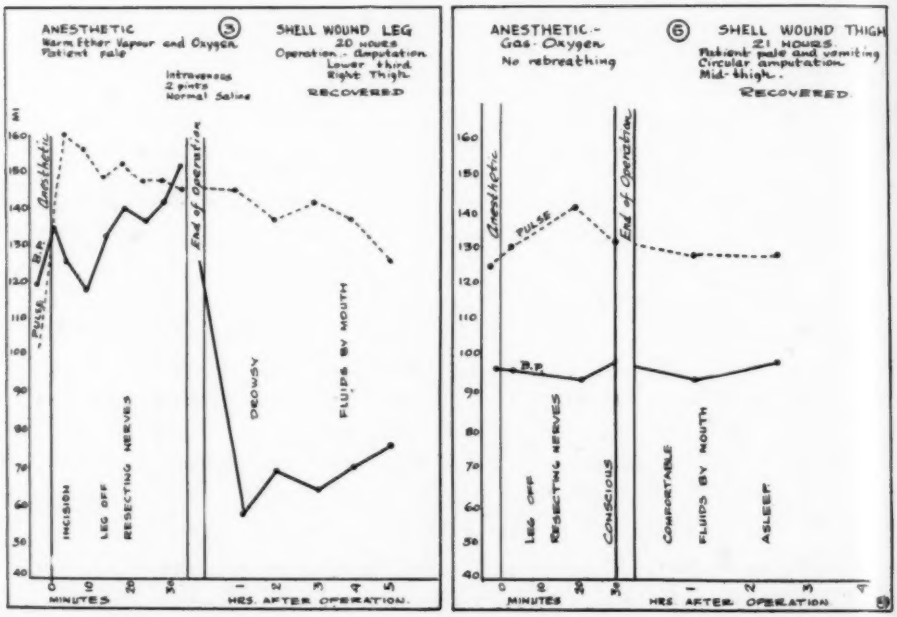


Fig. 17.—Comparison of the clinical effects of thigh amputation under ether with those of a like operation under nitrous oxid anesthesia. (Charts of wounded soldiers treated at Base Hospital, through the courtesy of Capt. Geoffrey Marshall.)

for an instant on the application of an intense stimulus, such as tearing of the abdominal wall, but there followed an equally abrupt fall, and the tendency was constantly downward.

The exposure of the viscera contributed to the precipitate decrease in the temperature of the brain, which will be noted in some of the

7. Crile, G. W.; Hosmer, H. R., and Rowland, A. F.: Thermo-Electric Studies of Temperature Variations in Animal Tissues, I. General Considerations; Description of Apparatus and Technique, Am. J. Physiol. **62**:341-348 (Oct.) 1922.

charts (Fig. 14). In these, the like fall in the temperature of the liver must probably be largely attributed to the direct exposure of the organ.

E. CLINICAL EVIDENCE

The clinical observations have been presented in previous volumes and papers; they are seen daily and were observed on a vast scale during the war (Figs. 15 and 16).

Of prime significance is the fact that methods of prevention indicated by these studies are successfully protecting our patients from the destructive results of the physical trauma of surgical operations. If physical trauma were the only injuring factor present in a surgical operation, its destructive effects could be modified, as our experiments have shown, by the use of local anesthesia and of nitrous oxid-oxygen. That exhaustion of the brain is the primary factor in the production of shock from surgical trauma is evidenced daily in the clinic by the protection afforded by these two agents (Fig. 17).

A later section of these studies in exhaustion will give further experimental evidence regarding the direct influence of these and other protective and restorative agents.

GENERAL SUMMARY

1. The effects of physical injury, especially of abdominal trauma, have been studied by (*a*) observations of the blood pressure; (*b*) measurements of the constituents of the blood; (*c*) histologic studies; (*d*) measurements of the H-ion concentration and of the alkali reserve of the blood; (*e*) estimations of the iodin content of the thyroid gland; of the epinephrin content of the suprarenals and the epinephrin activity; of the pituitrin activity; of the glycogen content of the liver and of voluntary muscle; (*f*) measurement of the electrical conductivity of the brain and the liver; (*g*) direct measurements of the temperature of the brain and the liver; and (*h*) clinical observations of patients after physical trauma received by accident or in war, or in surgical operations.

2. All of these lines of investigation indicate that changes in the central nervous system—primarily in the brain—constitute the fundamental cause of the exhaustion and shock which follow physical trauma.

3. The experimental evidence indicates that the liver, and possibly the suprarenals, is linked with the brain in the cycle of exhaustion-producing changes which are initiated by the changes in the brain.

4. These studies present no evidence that any primary change in the distribution or constitution of the blood is produced by physical trauma alone. When such changes were demonstrated, they were end-effects, not causative factors, of shock or exhaustion.

5. A limited group of experiments indicates that, under anesthesia at least, the suprarenals do not respond to the stimuli of physical trauma by any increase in their output.

6. The essential cause of exhaustion from physical trauma is identical with that of exhaustion from insomnia, by emotion and by exertion, as presented in the preceding studies in this series.

THE ETIOLOGY OF URINARY LITHIASIS: AN EXPERIMENTAL STUDY*

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In a recent study of the literature on the etiology of urinary lithiasis and closely related subjects, the conclusions reached after careful analysis may be summarized briefly, thus:

1. The problem of calculus formation in the urinary tract is one of chemical precipitation. The mechanism which causes the precipitation of urates, oxalates, phosphates, and so forth, in such a way that a fused hard concretion arises, rather than the deposition of individual crystals which maintain a state of isolation in passing through the urinary tract must be determined.

2. Differences in reaction, as determined by the hydrogen ion concentration, and qualitative and quantitative changes in the urinary colloids (such as pigments, mucin, nebecula, albumin, and nucleo-albumin), have been shown to influence the nature of urinary sediments both chemically and physically. The microscopic and gross features of calculi would seem to show that an abnormal variation of these factors is at work in the formation of stone.

3. Race, age, heredity, trauma, occupation, diet, sex, and geographic distribution seem to suggest little with regard to the etiology of concrements; if factors at all, they are probably of secondary importance.

4. The three commonest diseases associated with an increase in the crystalline content of the urine, namely, gout, oxaluria, and phosphaturia, are found far oftener without accompanying calculus deposition than with it. Many observers have assumed that there is a high incidence of lithiasis in such diseases, but have offered little statistical evidence to support their views.

Xanthinuria and cystinuria are necessary to the formation of xanthin and cystin stones, but the frequency with which xanthinuric and cystinuric patients escape calculus formation is problematic.

5. On the whole, clinical evidence points to a local mechanism at work in the kidneys, ureters, or bladder to cause the stones. The frequent occurrence of demonstrable foci of infection in patients suffering from calculus and the almost universal finding of infected kidneys

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the Degree of Master of Science in Pathology. The work was done in the Section of Experimental Surgery of the Mayo Foundation and the Section of Urology of the Mayo Clinic.

or bladders associated with stone lend weight to the belief that a specific stone-forming infection is at work in most instances. It is conceivable that at times excessive excretion of crystalloid material may reach such a degree that the normal protective colloids of the urine cannot handle the extra burden. Under such circumstances fusion of crystals and calculus formation might take place. Likewise, it is possible that qualitative or quantitative changes in the colloids of the urine may occur without bacterial infection. Such changes might lead to concrement formation even though the urinary crystalloid excretion remains within normal limits.

6. There is little direct evidence to prove that anatomic factors or stasis can initiate the stone-forming process; but their frequent association with calculus makes it seem likely that the stone-forming mechanism may work to better advantage under such circumstances.

The commoner theories of calculus formation were subjected to laboratory experimentation whenever possible, the procedures being guided to a high degree by the preceding studies. The magnitude of such a task is obvious and necessarily prohibitive so far as concerned many details which, though important, were not deemed immediately expedient. Abstracts of experiments are accompanied by typical protocols when necessary to afford detail.

SERIES 1. THE EFFECT OF A HIGH CALCIUM DIET ON THE CRYSTALLINE CONTENT OF URINE

A high content of calcium in the diet has long been considered a factor predisposing to lithiasis. For this reason an effort was made to concentrate the calcium salts in the urine of rabbits by administering massive doses of calcium oxalate, chlorid, lactate, and phosphate to normal rabbits, and also to rabbits that had been subjected to a low-grade toxic nephritis by the administration of minute doses of oxalic acid, mercuric chlorid, cantharides, or chloroform.

Feedings 1 and 2 were given on alternate days for the purpose of keeping the urine alkaline. After one week Feedings 3 and 4 were given on alternate days for the purpose of keeping the urine acid. The seven rabbits lived from nine to fifty-four days, the reaction of the urine being fairly well maintained. Aside from an occasional calcium oxalate octahedron, no visible increase in the crystalline content of the urine was noted. Necropsy did not reveal lime deposits or concretions. The intramuscular injections had been poorly absorbed.

Feedings 1 and 2 were given on alternate days for one week, thus keeping the urine alkaline. Feedings 3 and 4 were then given on alternate days to the end of the experiment. The four rabbits lived from ten to twenty-four days, the reaction of the urine being fairly

TABLE 1.—Experimental Feeding of Seven Rabbits (Experiments 1 to 7)

Feeding	Material	Amount	Method of Administration
1	Sodium bicarbonate	1 gm.	By stomach tube
	Oxalic acid	0.1 gm.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium oxalate	0.5 gm.	
2	Calcium lactate	1 gm.	In solution by stomach tube
	Calcium chlorid	1 gm.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium oxalate	0.5 gm.	
3	Sodium benzoate	1 gm.	Orally, in capsules and in solution by stomach tube
	Oxalic acid	0.1 gm.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium oxalate	0.5 gm.	
4	Calcium chlorid	1 gm.	In solution by stomach tube
	Calcium lactate	1 gm.	
	Hydrochloric acid, 1 per cent. solution	20 c.c.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium oxalate	0.5 gm.	

TABLE 2.—Experimental Feeding of Four Rabbits (Experiments 8 to 11)

Feeding	Material	Amount	Method of Administration
1	Mercuric chlorid, 1:250 solution	1 c.c.	By stomach tube
	Acid sodium phosphate	1 gm.	
	Ammonium chlorid	1 gm.	
	Magnesium oxid	1 gm.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium phosphate	1 gm.	
2	Calcium chlorid	1 gm.	In solution and suspension by stomach tube
	Ammonium chlorid	1 gm.	
	Hydrochloric acid, 1% solution	20 c.c.	
	Magnesium oxid	1 gm.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium phosphate (neutral)	1 gm.	
3	Sodium bicarbonate	1 to 3 gm.	In solution and suspension by stomach tube
	Acid sodium phosphate	0.1 gm.	
	Magnesium oxid	1 gm.	
	Ammonium chlorid	1 gm.	
	Mercuric chlorid, 1:250 solution	0.5 c.c.	Injected intramuscularly
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium phosphate	1 gm.	
4	Calcium chlorid	1 gm.	In solution and suspension by stomach tube
	Calcium lactate	1 gm.	
	Calcium lactate	0.1 gm.	Suspension in glucose solution, injected intramuscularly
	Calcium phosphate	1 gm.	

well maintained. A moderate degree of albuminuria was noted. No visible increase in the crystalline content of the urine was observed. Necropsy did not reveal crystalline deposits or concretions.

Here forced feeding of materials from which ammonium magnesium phosphate is derived was made in an endeavor to cause deposition of triple phosphate. Mercuric chlorid poisoning is often associated with calcium deposit in the renal tissues, hence the value of the negativity of this experiment may be emphasized.

Experiments 16 to 20.—Five rabbits were fed as in Experiments 8 to 11, with the exception that 0.1 to 0.5 c.c. of chloroform was fed instead of mercuric chlorid. Chloroform was used because of its action on the renal epithelium. The five rabbits lived from eight to nineteen days. The visible crystalline content of the urine was not increased. Necropsy revealed marked degenerative change in the hepatic and renal epithelium. No lime deposits or urinary concretions were noted.

Experiments 21 and 22.—Two rabbits were fed as in Experiments 8 to 11, with the exception that 0.1 minim of tincture of cantharides was substituted in the place of mercuric chlorid. Cantharides was used because of its nephrotoxic effect. The two rabbits lived twenty-one and ten days, respectively. The visible crystalline content of the urine was not increased. Necropsy revealed degenerative changes in the renal and hepatic epithelium but no crystalline deposits or concretions.

Comment.—Forcing lime salts in massive doses does not cause visible increase in the crystalline content of rabbit's urine. These experiments are in harmony with the views of pharmacologists that an increased ingestion of calcium salts will not lead to a significant increase of calcium in the urine. This is good evidence against a "hard water" or "lime soil" factor in the etiology of stone.

SERIES 2. THE FORCED ADMINISTRATION OF OXALIC ACID AND ITS DERIVATIVES

Ebstein [1] had shown that uric acid administered orally to rabbits and dogs is destroyed in the metabolism; but it had long been known that the administration of oxalic acid would cause the appearance of calcium oxalate in the urine. Therefore, in different groups of animals, oxalic acid, sodium oxalate, and ammonium oxalate were fed in sublethal doses.

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1. Ebstein, W., and Nicolairer, A.: Ueber die experimentelle Erzeugung von Harnsteinen, Wiesbaden, Bergmann, 1891, pp. 149; Ueber die Ausscheidung der Harnsäure durch die Nieren, Arch. f. path. Anat. **143**:337-368, 1896; Ueber die Wirkung der Oxalsäure und einiger ihrer Derivate auf die Nieren, ibid. **148**:366-388, 1897.

Two rabbits (Experiments 25 and 26) were fed 0.4 gm. of oxalic acid and 0.4 gm. of acetamid, daily, by stomach tube. As the feeding of diamido-oxalic acid had been shown by Ebstein to produce concretions, it seemed best to exclude the possibility of the amid group as a factor in concrement production. The two rabbits lived twenty-four and thirty-eight days, respectively. A moderate number of calcium oxalate crystals was noted daily in the urine. These crystals were always single, of the perfect octahedral type, and showed no tendency toward coalescence or fusion.

In Experiment 25, at necropsy, deposits of white material were found in the straight tubules in the renal pyramid. When scraped with the knife and examined microscopically these proved to be made up of calcium oxalate crystals of the octahedral type, without tendency toward fusion. Both animals showed slight vascular injection of the kidneys and epithelial degeneration in the tubules. No deposits or concretions were noted.

Two rabbits (Experiments 13 and 14) were fed 0.5 gm. of ammonium oxalate, daily. One rabbit (Experiment 27) was fed 1 gm. of ammonium oxalate and 1 gm. of acetamid, daily. The animals lived forty-seven, ten, and fifteen days, respectively. No visible increase in crystalline content of the urine was noted aside from an occasional calcium oxalate octahedron. Necropsy revealed slight nephritis but no crystalline deposits or concrements.

One rabbit (Experiment 15) was fed 0.5 gm. of sodium oxalate every two days; it died after forty-six days. A moderate number of calcium oxalate crystals of the perfect octahedral type were noted daily. These did not show a tendency to fusion. Necropsy revealed the kidney contracted with nephritis. No lime deposits or concretions were found.

SERIES 3. EFFECT OF ADMINISTRATION OF BUTYL OXALATE

Inasmuch as the oxaluria produced in Series 2 was not apparently intense, it was decided to feed an ester of oxalic acid in the hope that it would be less toxic than soluble oxalates, as it would furnish a lower concentration of oxalate ions. Ethyl oxalate, when given intramuscularly in doses of 0.5 c.c. or more, killed the animals almost immediately.

Experiments 28 to 33.—Butyl oxalate was injected intramuscularly into six rabbits in doses of from 0.5 to 1 c.c., daily. In several instances sodium oxalate was fed simultaneously in doses of 0.4 gm., in capsules, daily. The rabbits lived from four to nine days. All developed an intense oxaluria. In all the experiments except Experiment 28, the calcium oxalate crystals were perfect octahedrons, showing no tendency toward coalescence or fusion.

In Experiment 28, after receiving butyl oxalate and sodium oxalate, daily, for six days, the animal died spontaneously. Marked oxaluria with dumb-bell shaped crystals and atypical octahedrons was noted. At necropsy marked distention of the intestines and injection of the mucosa were noted. The bladder was congested and distended and contained about twenty small smooth white stones about 1 by 2 mm. in diameter. On chemical examination these proved to be calcium oxalate. As this was the first experiment of the series, cultures were not taken, and sections of the tissues were not made. The kidneys appeared slightly injected but otherwise normal. All efforts to repeat the experiment proved futile.

Comment.—The association of an atypical crystalline oxaluria with formation of concretions was noted in one instance, while the remaining animals consistently showed a typical octahedral form of calcium oxalate in the urine with no concrement formation. This suggests that a change in crystalline form may be related to concrement formation.

SERIES 4. THE RESULT OF PLACING AN ORGANIC NUCLEUS IN THE RENAL PELVIS OF THE RABBIT

The presence of organic nuclei, such as fragments of epithelium and disintegrating tissue, having been observed in many calculi, it was decided to determine the effect of placing pieces of tissue into the pelvis of the rabbit's kidney.

Experiments 102 to 105.—In four rabbits under ether anesthesia and aseptic technic, the left kidney was removed through a lumbar incision; a wedge-shaped portion of the renal pyramid, not quite large enough to fill completely the cavity of the pelvis, was excised. This was placed gently in the renal pelvis, the kidney carefully sutured with No. 00 plain catgut, and the incision closed in layers. The animals lived from six to 121 days; they were killed after the longer periods. In all cases at necropsy the piece of tissue was found lying in a pool of urine and undergoing disintegration. In Experiment 102, when the animal was killed, the pelvis was found clear, no trace of the tissue being seen. There was no evidence of calcareous deposit, and, except for the operative scar, the kidney appeared normal. A culture was negative for bacterial growth.

In view of this negative result, bits of muscle and fascia from the lumbar region were introduced through a nephrotomy wound into the left renal pelvis of several rabbits. The kidney and the incision were closed. Several of the animals are still alive. In Experiment 108 the animal was killed 122 days after operation. The disintegrating muscle tissue was found to be impregnated with lime salts lying in a pool of purulent material; the kidney showed moderate hydronephrosis. A

culture of the pus yielded a gram-positive bacillus. One half of the muscle tissue was firm and stony, while the other half was soft and gritty.

Comment.—No conclusions can be drawn from a single experiment; but it would seem that foreign bodies or organic nuclei in themselves will not initiate stone formation. If retained long enough, however, they may form a point of lowered resistance for bacterial invasion by irritation. Under such conditions they become impregnated with crystalline material which may develop into true calculi. In the cases in which bits of renal pyramid were enclosed in the pelvis, cultures were negative. Infection was not determined by culture from several animals that died within a week after the insertion of the muscle tissue into

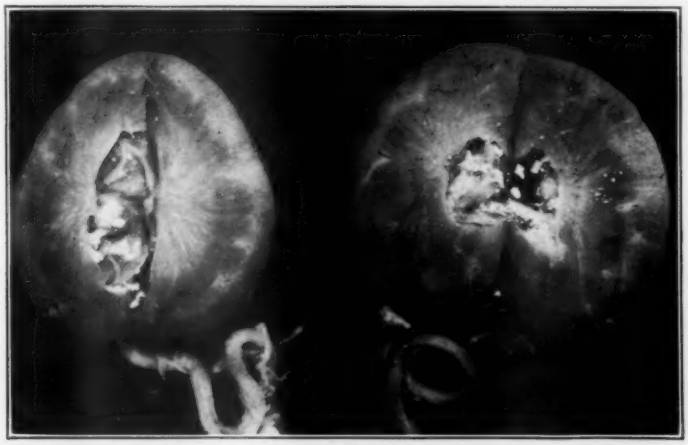

Fig. 1. (Experiment 58).—Bilateral lithiasis in a rabbit fed oxamid daily for seventeen days; larger masses lie behind the free margin where the calices are attached to the renal parenchyma (Fig. 13).

the pelvis of the kidney. Filling the pelvis with bits of muscle tissue is equivalent to the introduction of stasis of high degree and also to increasing markedly surface duplication in the pelvis. Hence it would seem that the failure to secure a deposit of crystalline material in the absence of infection is a strong point against a purely mechanical theory of stone formation.

SERIES 5. A STUDY OF THE FORMATION OF OXAMID CALCULI

The formation of concretions in the urinary tract after the administration of oxamid to animals had apparently been regarded as a medical curiosity since the time of Ebstein, although subsequently Tuffier [2] and

2. Tuffier, M.: Lithiase urinaire artificielle, Bull. Soc. anat. de Paris **68**:49-53, 1893.

Rosenbach [3] had carried out confirmatory experiments. Little or no mention of the process occurs in current literature, especially in this country. The fact that oxamid would form urinary concrements had been confirmed in Mann's laboratory by J. R. McVay, who had fed two dogs on oxamid for several months. Hence it was decided to study this phenomenon more in detail with the hope that the observations might give an insight into the genesis of calculi seen clinically.

Fourteen rabbits (Experiments 56 to 69) were fed oxamid orally in capsules in doses of 0.4 to 0.8 gm., daily. Five dogs (Experiments 118 to 122) were fed oxamid in doses of 2 gm., daily, by the same method. The results are given in Table 3.

TABLE 3.—Experimental Feeding of Fourteen Rabbits and Four Dogs

Rabbits Experiment	Duration of Life, Days	Oxamid Fed, Gm.	Cause of Death	Sediment, Concretions, and Location Found at Necropsy
56	10	8	Coccidiosis, nephritis	Two minute concretions in right pelvis; sand in left
57	10	8	Nephritis	A few particles of sand in left pelvis; stone in the bladder
58	17	11	Nephritis	Minute concretions in both pelves (Fig. 1)
59	7	4.8	Nephritis	Fine sand in right pelvis; left clear
60	18	12.8	Nephritis	Fine sand in calices of both sides
61	26	13.4	Nephritis	No deposit
62	17	9.6	Nephritis	Right pelvis clear; a few flecks of sand in left
63	26	9.6	Pneumonia	No deposit
64	10	8	Pneumonia	A few flecks of sand in right pelvis; left clear
65	41	28	Accidental	Slight amount of fine sand in both pelves
66	7	10	Accidental	No deposit noted
67	20	28	Ether	Small stone in right ureter and sediment in right pelvis; slight deposit in left pelvis
68	20	28	Ether	A few flecks of sand in right pelvis; left clear
69	25	20	Pneuomnia	Right pelvis clear; kidney shows crystalline infarcts in left pyramids; a few small stones
Dogs Experiment	Months and Days			
118	9 5	130	Ether	No deposit noted *
119	5 10	140	Accidental	Stones in right kidney; left clear; hydronephrosis
120	7	324	Nephritis	Stones in both kidneys and ureters
121	36	40	Pneumonia	Small stones in both kidneys
122	14	20	Pneumonia	Crystalline infarcts in right kidney; few small stones in right pelvis, left clear

* Oxamid not given three months before death.

After an interval varying from a few days to several months, yellow crystalline material, varying from traces of fine sand to concretions 1 cm. in diameter, appeared irregularly in the kidneys, ureters, or bladder of about 75 per cent. of the animals. Concrements of sufficient magnitude to be considered stones occurred in about 50 per cent. of the animals. Smaller deposits were the rule. The deposit often was bilateral, with no preference as to side. The larger concretions showed definite radial striations and concentric markings suggestive of deposi-

3. Rosenbach: Kritischer und experimentelle Beiträge zur Frage der Entstehung der Nierensteine, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **12**:630-656, 1911.

tion in layers (Fig. 2). The deposits were more often multiple than single. Five animals (about 25 per cent.) did not have deposits after long feeding. The passage of sand and smaller concrements was found in all animals from which twenty-four hour specimens of urine were collected by means of metabolism cages. Cultures from the kidneys and from the urine were consistently sterile. The animals often lost weight, especially on long feeding. All showed variable toxic degenerative changes in the epithelium, and increase in the vascular injection of the liver and kidneys. The liver especially was firm, with an increase in fibrous tissue in the experiments of longer duration. No intracellular crystalline deposits or stones in the renal parenchyma were noted Albuminuria, without pus, casts, or red cells, was a constant finding. In several instances, an atypical reduction of Fehling's solution was observed, but a true glycosuria was never demonstrated.

The reaction of the urine, as roughly determined by litmus, seemed not to affect the process; some of the animals had acid urine, others

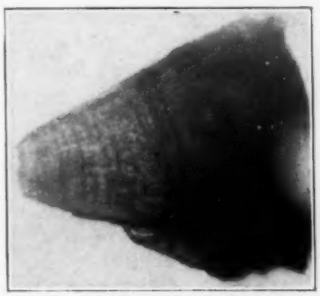

Fig. 2.—Fragment of an oxamid stone showing radial markings and the deposition in concentric layers; × 200.

alkaline. Three rabbits (Experiments 78 to 80) were fed 1 gm. of sodium benzoate, daily, with the oxamid; the urine was usually acid; two had a moderate amount of oxamid deposition. Four rabbits (Experiments 81 to 84) were fed 1 gm. of magnesium oxid, daily, with the oxamid; the urine was consistently alkaline. One of the animals developed definite concretions in the kidney and others showed traces of sand.

Extending the duration of feeding, increasing the daily dosage of oxamid to 10 gm. (Experiments 67 to 76), varying the fluid intake in twenty-four hours (Experiments 69 to 75) seemed not to produce, within wide limits, quantitative change in the amount of oxamid deposition found in the urinary tract at necropsy. (On complete withdrawal of water the excretion of oxamid decreased as the experiment approached termination.) Toxic nephritis produced by mercuric chlorid (Experiments 85 and 86) likewise had no apparent effect on the process.

The Crystallographic Features of Oxamid Lithiasis.—In a former publication [4] it was noted that Rainey,[5] Ord and Shattock [6] and others have suggested a relationship between calculi and abnormal crystalline forms which had occurred when the crystalline material was deposited from gelatinous or colloidal mediums. Within from twenty-four to thirty-six hours after the feeding of oxamid to animals, abnormal crystals appeared in the voided urine. These were variously pigmented, the color ranging from a light brown to a brownish black. The crystals were doubly refractile in the dark field where the brownish-black color was found to be really a deep orange. The morphology of the crystals can be appreciated readily by referring to Figures 3 to 6. Many of the crystals were isolated and single. Others were clumped together somewhat after the manner of agglutinated blood cells. However, dotting the

Fig. 3 (Experiment 61).—Different phases of crystalline morphology in sediment of a rabbit fed oxamid, simple crosses, crosses with the interbrachial spaces partly filled, square forms, and spherical forms; × 200.

field in numbers varying with the specimen were masses of crystals in every degree of coalescence and fusion. There were, in the different specimens, a number of morphologic varieties of crystals. All seemed to be developed from a simple crosslike form (Figs. 2 and 3). There were crosses with smooth arms and crosses with rough pointed arms;

4. Keyser, L. D., and Braasch, W. F.: The Etiology of Urinary Lithiasis: Collective Review, Surg., Gynec. & Obst., Internat. Abst. Surg. **34**:1-10, 1922.

5. Rainey, G., quoted by Ord, W. M., and Shattock, S. G.: On the Microscopic Structure of Urinary Calculi of Oxalate of Lime, Tr. Path. Soc., London **46**:91-132, 1895.

6. Ord, W. M., and Shattock, S. G.: Footnote 5, second reference. Shattock, S. G.: On the Microscopic Structure of Uric Acid Calculi, Proc. Roy. Soc. Med. **4**: Path. Sect. 110-146, 1911.

crosses with the interbrachial spaces roughened and partly filled out; squared forms which seemed to be crosses with the interbrachial spaces entirely filled, and, finally, spheres, rough and smooth on their surfaces. These seemed to be a rounded variety of the squared form and the end-product of development of the cross. The perfect smooth sphere appeared umbilicated and radially striated (Figs. 5 and 6). The size of the crystals varied from microscopic dust to crystals from 40 to 50 microns in diameter. All the varieties of crystal form were found in states of fusion to some degree; but in this connection several features

Fig. 4 (Experiment 61).—Little tendency to fusion of crystals in urine of a rabbit fed oxamid; at necropsy there was no deposit in kidneys or bladder; × 150.

were noted early and were confirmed by a daily study of urinary sediments from many animals.

There was a tendency for all the forms to coalesce and fuse; but this was greater the more nearly the crystal approached the spherical form. Likewise, the smaller the crystal and the lighter its pigmentation the more often was it found fused with other crystals. The converse was also true. The closer the crystal approached the cross form, the larger it was, and the greater its pigmentation, the greater were its chances of being isolated and unfused with other crystals.

Smaller concretions found in the kidney or passed in the urine were found to be made up of crystals of the type just described. In the larger concretions the individuality of the crystals was found in some degree to be lost; but even here on crushing the stone, particles resembling crosses and spherical forms were observed (Fig. 7).

Every animal fed on oxamid passed almost all the different morphologic varieties of crystal types; but there was a great tendency for one type or the other to predominate. Depending on this, to some degree, was the likelihood of finding calculi in the kidneys at necropsy. Putting this in another way, it was noted that animals with urine in which small, light-pigmented, smooth or rough spheres predominated would show

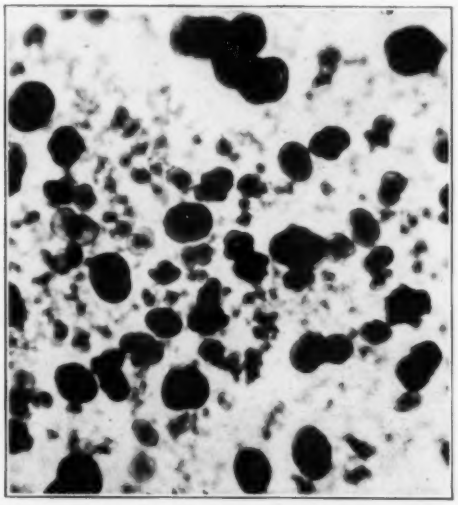

Fig. 5 (Experiment 68).—Large smooth spheres showing a tendency to remain isolated. From the urine of a rabbit fed oxamid; × 100.

larger particles of sand in their twenty-four hour specimens, and the deposits found at necropsy would be of the larger, harder type. However, the animal with a predominance of large, dark-brown spheres or crosses alone (associated with few spheres in the microscopic field) would pass only finer particles of sand and would present only fine grains of sand or smaller soft concretions in the urinary tract at necropsy. Thus there seemed to be some relationship between the type of crystal and the size and kind of calculus formed.

The Chemistry of Oxamid: Its Reactions in Urine: The Chemistry of Oxamid Stones.—A rather superficial study of the chemistry of oxamid and its reactions in vitro in the urine of normal animals and of human beings has given some results which appear to me especially

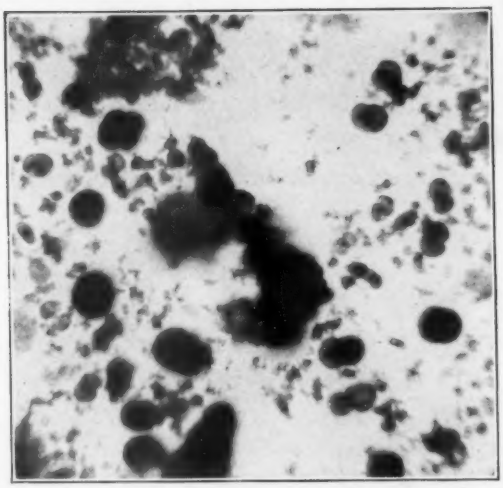

Fig. 6 (Experiment 68).—Agglomerations of small, light colored crystals from urine of a rabbit fed oxamid; the larger dark crystals tend to remain isolated; × 100.

Fig. 7 (Experiment 68).—A large agglomeration or beginning calculus composed of small spheres and crosses in urine of a rabbit fed on oxamid; × 100.

enlightening in their relationship to the formation of oxamid stone. Oxamid is the diamid of oxalic acid, having the formula $\begin{matrix}CONH^2\\|\\CONH^2\end{matrix}$. While insoluble in cold water, it goes into solution slowly in boiling water and is gradually hydrolyzed by further boiling to ammonium oxamate and later to ammonium oxalate. Acids or alkalis hasten this hydrolysis. As prepared synthetically by treating an oxalate ester with ammonia, it consists of small irregularly rhomboidal, fissured, translucent, colorless crystals which at times show split and roughened ends (Fig. 8).

Oxamid stones, as has been noted, show all degrees of structure from fused aggregations of crystals, individual units of which may be

Fig. 8.—Crystals of pure oxamid synthetically prepared; × 300.

distinguished on crushing and examining under the microscope, to more solid, completely fused forms in which the identity of the individual crystals is almost, if not quite, lost.

These concretions give the reactions of oxamid, yielding ammonium and oxalate ions on prolonged boiling in water or on dissolving in acid or alkali. They also contain an organic pigment material the identity of which has not yet been established.

Effect of Urine in Vitro upon Morphology of Oxamid Crystals.—Synthetic oxamid heated with urine of human beings dissolves at from 90 to 100 C. in an average quantity of 50 mg. to 10 c.c. of urine. Part of it is undoubtedly hydrolyzed and is not reprecipitated on cooling.

However, some of it is reprecipitated, and this precipitate examined microscopically gives a surprising result. The crystals have become pigmented and have assumed the forms which we have noted in the crystals passed in the urine of animals fed on oxamid. Also there is a corresponding visible diminution in the pigmentation of the urine from which the crystals have been precipitated. All types of oxamid stone-forming crystals have been noted under such conditions from the simple cross to the sphere (Figs. 9 and 10).

If the artificially prepared stone-forming crystals or the sediment from the urine of oxamid-fed rabbits is boiled with water, a clear pigmented solution is obtained. If this solution, while hot, is filtered several times through a heated charcoal filter, the pigment and possibly

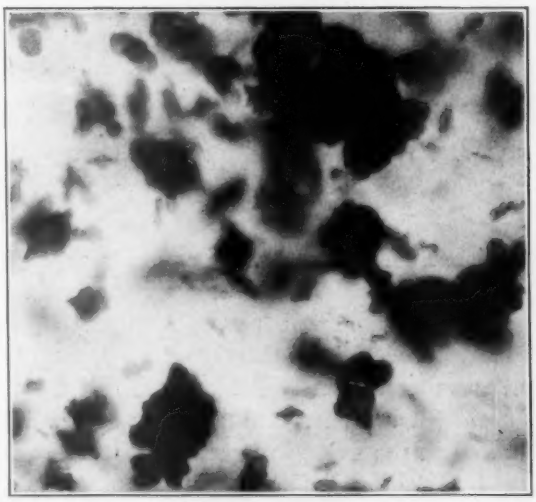

Fig. 9.—Deposit obtained when synthetic oxamid is dissolved in boiling urine and allowed to precipitate on cooling. The crystals are the developing-cross type; they are pigmented and show marked tendency to fuse into small agglomerations. This sediment is indistinguishable from that in the urine of rabbits fed on oxamid (Fig. 7); × 300.

other organic colloids are removed. If this is done from ten to fifteen times, the precipitate obtained on cooling comes to assume an entirely altered form. The crystals are colorless and approach very nearly the form of synthetic oxamid crystals.

Formation of Fusing Oxamid Crystals from Urine in Vitro.—An experiment which seemed to answer the question with regard to the process of the formation of oxamid stone consisted of repeated precipitation of increments of oxamid from the urine of human beings or of animals into the same test tube over a period of days, thus obtaining

fusion of crystals. Small concretions have been produced which microscopically and chemically, judged by simple tests, resemble small oxamid concretions found in the urinary tract of animals fed with the drug (Fig. 11).

Comment.—The process that takes place in the urinary tract of the animal may be repeated in the test tube, and, further, it is possible to extract, by a sort of fractional absorption, the pigment material from the crystals deposited by oxamid-fed animals, under which conditions a reversion to a simpler crystalline form takes place. Whether the pigment alone is responsible for the change, or whether there are other organic materials present, has not been determined. However, one conclusion may be held as established: The oxamid concretion is the product of a normal colloidal mechanism of the urine; in other words, oxamid being secreted into the urine of animals is precipitated so that a loose physicochemical union with organic materials (probably normally present in the urine) takes place. As a result of this unstable union the crystalline form is changed and individual crystals tend to coalesce with one another and become fused. I have seen this process in every stage, both in the test tube and in the urine of oxamid-fed animals. It speaks emphatically for a colloidal precipitation mechanism in the formation of concrements.

The action of normal urine is specific so far as causing fusion of oxamid crystals is concerned. This is certainly not the case with crystals of oxalates, urates, and so forth, passed normally by human beings. The urinary colloids tend to keep these crystals separate, unfused, and isolated under normal conditions. But oxamid is a crystalline material foreign to the normal urinary tract, and the only crystalloid known that can be concentrated in the urine in massive amounts over an extended period of time by feeding. The oxalate experiments most nearly approached this; but oxaluria was not obtained in any degree comparable with oxamiduria. Once by forcing the dosage of butyl oxalate, abnormal crystals and concretions were obtained, but this experiment could not be repeated.

That the sole factor is not the intensity of the oxamiduria is shown by the fact that the animals formed concrements in a short time, and with small doses. Within wide limits the dosage or duration of feeding seemed to play little part. Hence it must be assumed that the urine is unable to handle oxamid excretion. The very colloids that enable it to carry in solution uric acid, oxalates, phosphates, and so forth, may cause it to throw the foreign oxamid from solution in the form of crystals in all states of fusion.

This conception of the formation of oxamid stone differs entirely from that of Ebstein, who believed that the oxamid was retained in the cells of the straight tubules of the kidney and that its deposition around

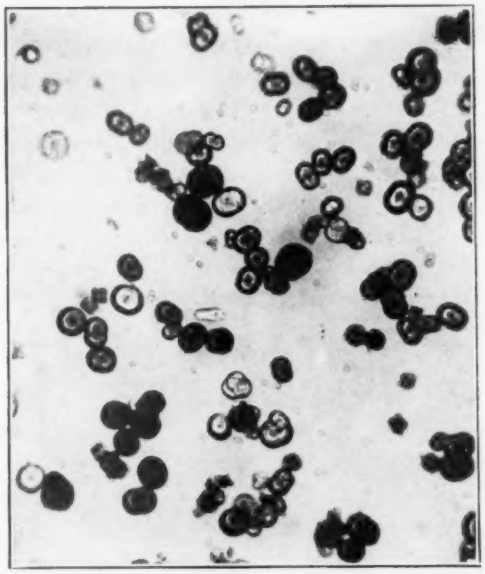

Fig. 10.—Oxamid crystals deposited in vitro from urine in which the synthetic chemical was dissolved by boiling; showing the perfect smooth sphere and no tendency to fusion; × 200.

Fig. 11.—A small oxamid concrement formed, in vitro, by repeatedly precipitating oxamid from human urine. This is a dense form indistinguishable from particles shown in Figure 7; × 50.

these dying cells gave origin to stones. In this investigation intracellular deposits of oxamid in microscopic sections, either with fresh frozen tissue, with frozen fixed tissue, or with paraffin sections, were not seen; neither was epithelial débris impregnated with oxamid noted. Ebstein probably paid more attention to the toxic nephropathy than to the crystallography of oxamid in urine and to this may be attributed the difference in results.

The deductions made for the oxamid concrement formation are obviously entirely in harmony with the work of Rainey, Ord and Shattock, Fowler,[7] Schade,[8] and with clinical experience with urinary, biliary, and other concrements.

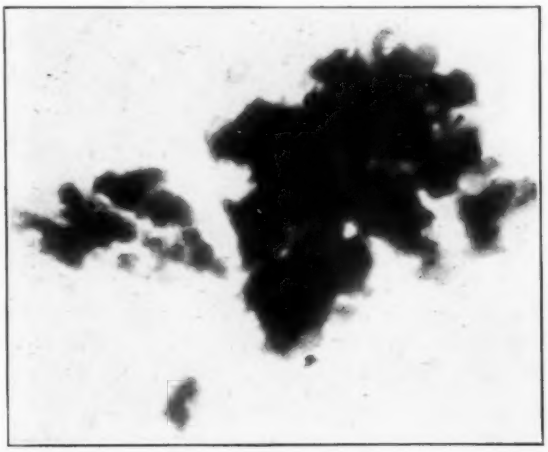

Fig. 12 (Experiment 68).—A small crushed concrement in the urine of a rabbit fed oxamid. It consists of small light colored crystals which have coalesced and fused; × 100.

SERIES 6. A STUDY OF ANATOMIC OR MECHANICAL FACTORS IN THE PRODUCTION OF OXAMID CALCULI: A POSSIBLE CLINICAL ANALOGY

After the type of mechanism fundamentally at fault in the production of oxamid calculi had been established, by analogy it was suggested that an abnormal colloidal mechanism in the urine is at work primarily in the formation of concrements seen clinically. Therefore, it became a matter of immediate interest to see how anatomic or mechanic factors would alter the picture, thus throwing light on the reason why stasis, diverticula, organic nuclei, and duplication of surfaces are so often associated with stone, but are also more often unassociated.

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7. Fowler, H. A.: The Microscopic Structure of Urinary Calculi of Oxalate of Lime, with Special Reference to the Spiculated Variety, Johns Hopkins Hosp. Rep. **13**:557-569, 1906.

8. Schade, H.: Beiträge zur Konkrementbildung. I. Zur Entstehung der Harnsteine, München. med. Wchnschr. **56**:3-7; 77-80, 1909.

It should be recalled that only 50 per cent. of the animals presented stones at necropsy, and 25 per cent. showed no trace of oxamid deposit. Two animals fed for as long as twenty-six days showed no deposit; another fed for six months died three months later. No oxamid deposit was found. It should also be recalled that undoubtedly most of the small fused masses of oxamid crystals are washed on and voided with the urine. Furthermore, every animal fed on oxamid presented sand in the urine at some time or other, while in all states of fusion crystals were consistent, the degree of fusion depending on the crystal type predominant. What then causes the retention of the precipitate that is

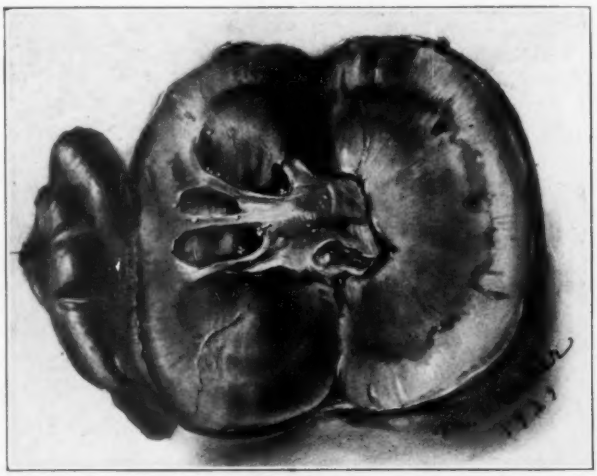

Fig. 13 (Experiment 121).—Kidney of dog fed on oxamid showing how the calices are attached to the renal parenchyma in kidneys of the dog and rabbit. The little pockets behind the free margins are the first sites of oxamid deposition.

to grow to the larger stone? Obviously, stasis, diverticula, and surface duplication, as powerful accessory factors in holding back the fusing crystals, are to be considered. In proof of this conception, so far as it relates to the oxamid calculus, the following observations are offered:

1. The first site of deposition of oxamid in the kidney of the dog or rabbit was invariably in the ramifications of the calices, along the line of attachment of the pelvis to the renal sinus. In the rabbit and dog, there is a tiny pocket behind the cusp of the free margin of the calix (Fig. 13) in which the concretions were usually found. This is duplicated surface and a point where the normal urinary stream and the musculature of the pelvis probably exert less force in washing crystalline material onward. The tendency of smaller urinary concrements in human beings to lie in the minor calices should be recalled in this connection.

2. (Experiments 91 and 92). Under ether anesthesia and with aseptic technic the left kidney of the rabbit was delivered through a lumbar incision and the renal pelvis exposed. With a fine needle, twenty punctures of the pelvis were made in different areas, care being taken to pierce through and through each time. The bleeding was controlled, the kidney replaced, and the wound closed.

On feeding oxamid to two animals thus treated, an excess of deposit of oxamid and large concretions were found on the left or traumatized

Fig. 14 (Experiment 96).—Marked deposit of oxamid in left kidney of a rabbit fed oxamid nine days as the result of low-grade stasis caused by rubber band around the left ureter. The untreated right kidney is clear.

side; on the untreated right side, no deposition was found in either instance. Here the pelvis was roughened and produced a minute duplication of surfaces, in all probability with microscopic diverticula. Cultures from the kidneys of both of these animals were entirely negative.

3. In order to determine the effect of hydronephrosis and stasis alone, a rubber band was placed around the left ureter so as to constrict it slightly (Experiment 93). The animal was fed 0.8 gm. of

oxamid, daily, for eight days. At necropsy hydronephrosis on the left side without oxamid deposit was found. This was also found to take place in several preliminary experiments, which were performed in trying to establish the technic. Hence it was concluded that the ureter on the left side had been constricted to such an extent as to interfere with the pressure equilibrium of urinary secretion; thus, neither the oxamid nor other material had been secreted on that side. The technic was then modified. A left abdominal incision was made, the left ureter

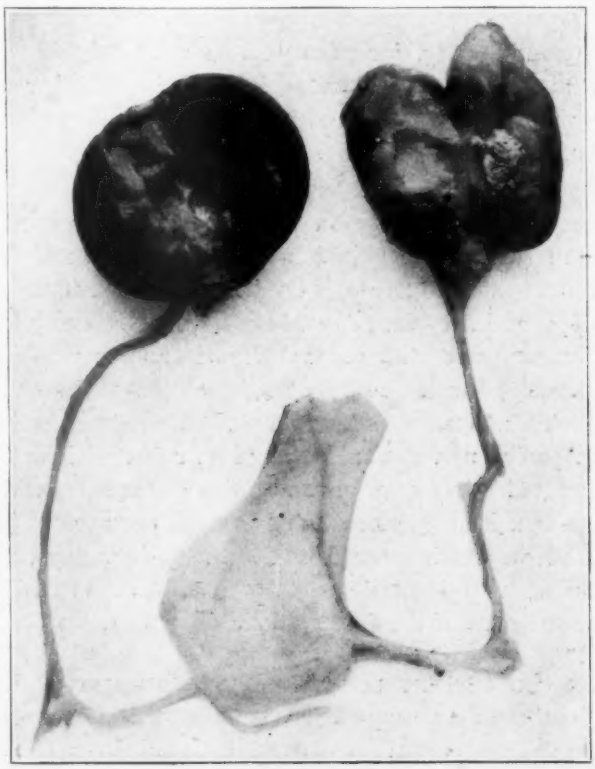

Fig. 15 (Experiment 90).—Kidneys of a rabbit fed oxamid, showing the formation of an oxamid calculus around an organic nucleus or foreign body (muscle tissue), previously placed in the left renal pelvis. A striking example of the rôle played by stasis, duplication of surfaces, and minute diverticula. The right untreated kidney is clear.

exposed, and a rubber band placed snugly around the ureter. No effort was made to constrict the ureter. The periureteritis and swelling which took place in consequence of the presence of the foreign body (rubber band) was depended on to constrict the ureter slightly. On feeding oxamid to rabbits thus treated (Experiments 94 to 96), stones and a marked increase in deposition of sand on the treated side were obtained

consistently in a few days. On the untreated right side only a few flecks of oxamid were found in any instance. One animal (Fig. 14) had been fed only nine days. The treated left side was filled with sand and minute concretions. The untreated right side was clear. This is a striking demonstration of the rôle which stasis plays in the retention of fusing oxamid crystals and in the growth of oxamid stones.

4. In Experiment 97 the left kidney was opened with a nephrotomy incision. A piece of blood vessel silk was placed on the cut surface, running from the tip of the pyramid to the cortex. The free end was allowed to remain in the pelvis of the kidney. The animal was fed 0.8 gm. of oxamid, daily, for twenty-nine days. At necropsy the left kidney was filled with several small stones and the thread was encrusted with a deposit of oxamid. The right untreated kidney also contained deposit but much less than the left.

Experiments 88 to 90.—Under ether anesthesia the left kidney was exposed through a lumbar incision and a nephrotomy performed. Bits of muscle and fascia were placed in the renal pelvis and the incision closed. Three rabbits thus treated were fed on oxamid. They lived thirty days, nine days, and fifty-four days, respectively. In every instance the tissue became encrusted with oxamid deposit, and in Experiment 90 a concretion developed which entirely filled the renal pelvis and measured 0.5 by 1 cm. This concrement lay in a pool of pus from which a gram-positive staphylococcus was demonstrated on culture. The rabbits that lived for nine and thirty days gave negative cultures from the kidneys and urine. Hence it may be concluded that the presence of infection in Experiment 90, in which the animal lived fifty-four days, was due to secondary invasion of bacteria to the area of lowered resistance produced by the presence of the foreign body (Fig. 15).

SUMMARY OF CONCLUSIONS CONCERNING THE FORMATION OF OXAMID CALCULI AS DEDUCED FROM SERIES 5 AND 6

1. Oxamid fed to animals is specifically precipitated from the urine by a normal colloidal mechanism in such a way that the unit crystals tend to fuse, probably in loose chemicophysical union with certain of the colloids.

2. The concretions formed as the result of this fusion have the general physical features of calculi seen clinically.

3. The process is sterile at least at the beginning.

4. A considerable amount of the material thus deposited is passed on with the urine; but an occasional fragment is retained in the calices or at points where the adhesive force between the minute fragment and the epithelium of the urinary tract is great enough to resist the force of the urinary stream.

5. Duplication of surfaces, diverticula, stasis, hydronephrosis, of such a degree as not to upset markedly the pressure equilibrium of urinary secretion, and organic nuclei greatly enhance the chances of retention of the fusing crystals and in this manner foster the formation of larger stones.

6. Oxamid concretions while sterile at the outset probably act after a time as foreign bodies and invite bacterial invasion which may in turn cause an increase in concrement growth.

SERIES 7. THE INTRODUCTION OF INFLAMMATORY EXUDATES INTO THE URINARY STREAM BY MEANS OF EXPERIMENTAL RENAL INFECTION: THE INFLUENCE OF SUCH EXUDATES UPON THE DEPOSITION OF CALCIUM OXALATE AND THE PRODUCTION OF SMALL CONCRETIONS BY SUCH METHODS

After the mechanism of the formation of oxamid stones had been established, at least in principle, it was felt that an analogous process must take place in calculi seen clinically in human beings. In the urine of normal animals when the saturation limit for oxamid is reached (0.02 to 0.03 gm. for each 100 c.c.),[9] there is precipitation of fusing crystals. This is not the case with oxalates, urates, and so forth, which, their saturation limit having been reached, are precipitated as isolated, unfused units.

What if abnormal colloidal material such as that contained in pus or inflammatory exudates is introduced into the urinary stream? Will the normal precipitating mechanism of the urine be disturbed? Under such condition what will be the result of the concentration of oxalates in the urine in Series 2? Inflammatory exudates contain amino-acids, albumin, nucleoprotein, albumoses, proteoses, peptones, enzymes, lecithin, fat, cholesterol, and purin bodies, held for the most part in colloidal solution. Most of these materials are present in normal urine in traces or not at all.

Experiments 35 to 49.—Minute doses of colon bacilli (twenty-four hour and old cultures) were injected directly into the left kidney of rabbits by means of needle puncture; the kidney was located by palpation under anesthesia. Four-tenths gram of sodium oxalate was fed daily to thirteen rabbits. In Experiment 49, 0.5 c.c. of butyl oxalate was given daily. The fourteen rabbits developed suppurative pyelone-

9. In Experiments 67 and 68 the oxamid output was determined by hydrolysis to oxalic acid and quantitatively by means of a modification of the Autenreith-Barth technic for this material. The twenty-four hour specimens of urine contained from 0.02 to 0.03 gm. of oxamid (as oxalic acid) for each 100 c.c. after the sediment had been removed by filtration. (Brugsch, T., and Schittenhelm, A.: Technik der speziellen klinischen Untersuchungsmethoden, Berlin, Urban und Schwarzenberg, 1914, pp. 783-784.)

phritis which caused their deaths after a period varying from several days to two weeks. Three animals of the series (Experiments 35, 36 and 44) had atypical crystalline deposit in the calices; the largest deposit was about 0.5 mm. in diameter. Crystalline deposit was not found in the kidneys of the remaining animals. The crystalline morphology of the calcium oxalate excreted under such conditions has not yet been determined. In Experiment 49, in which butyl oxalate was fed after the injection of a stool culture from the rabbit into its own left kidney, a number of atypical crystalline particles were seen in the urine. However, no concretions were found.

SERIES 8. THE PRODUCTION OF A MINUTE CONCREMENT BY MEANS OF TRAUMA AND INFECTION

Cushing,[10] in 1899, traumatized the gallbladder of a dog and soon thereafter introduced into a vein an attenuated culture of typhoid bacilli. An acute cholecystitis ensued and minute concrements were found in the gallbladder. This suggested a similar experiment on the kidneys.

Experiment 50.—A left nephrotomy was made on a rabbit through a flank incision, under anesthesia and aseptic conditions. The renal pelvis was thoroughly traumatized by pinching with mosquito forceps; the kidney and wound were then closed. One cubic centimeter of a twenty-four hour culture of colon bacilli, which had been obtained from a calculus removed clinically, was injected into the vein of the ear. The rabbit died after eight days. Acute pyelonephritis and several small doubly refractile bodies, about 0.5 mm. in diameter, were found in the calices at necropsy. The crystalline bodies were not associated with the line of suture. Repeated efforts to duplicate this result (Experiments 51 to 54) have proved futile. Whether the strain of bacteria which was associated with the concrement in Experiment 50 was that of a specific stone-producing bacillus, which lost its power in subculture, or whether the concretions were encrustations on necrotic tissue is an open question. A conclusion cannot be drawn from a single experiment which cannot be repeated.

CONCLUSIONS FROM SERIES 7 AND 8

Inflammatory exudates are associated possibly experimentally with a change in morphology of calcium oxalate crystals when deposited in

10. Cushing, Harvey: Typhoidal Cholecystitis and Cholelithiasis. Discussion of a Possible Agglutinative Reaction of the Bile and Its Relations to Stone Formation, Bull. Johns Hopkins Hosp. **9**:91-95, 1898; Observations upon the Origin of Gallbladder Infections and upon the Experimental Formation of Gallstones, ibid. **10**:166-168, 1899.

urines containing such exudates. Several small concretions made up of atypical fused crystals have been observed under such conditions.

CONCLUSIONS FROM THE ENTIRE EXPERIMENTAL STUDY

1. The difficulty with which calcium salts, oxalates, urates, and other normal crystalline deposits of the urine are increased to any appreciable degree by various methods of administration has been pointed out. The only marked increase in visible crystals has been attained by feeding oxamid, a material foreign to the urine of animals. From this it would seem that an exogenous or dietary increase in crystalline materials would not produce a corresponding pathologic increase of these materials in the urine. On this basis, oxalurias, phosphaturias, xanthinurias, cystinurias, and excessive uric acid output must be more of endogenous than of exogenous origin. Some defect of metabolism by which the colloidal content or hydrogen ion concentration of the urine is altered, rather than a defect of diet, is at work.

2. Of the four methods by which artificial concretions have been obtained, only the feeding with oxamid gave consistent results. There were suggestive features in connection with the other experiments which pointed to the working of some abnormal precipitation mechanism.

3. Oxamid, a crystalloid foreign to the urinary tract, on being excreted, finds no mechanism present to keep its crystals separate as morphologic entities. Rather it is precipitated with colloidal material of normal urine in such a way that fusion of crystals and concrement formation ensue.

4. Mechanical factors are effective, at least, in the case of oxamid, in promoting retention of crystals and growth of the stones; but they are not essential to the process.

SUMMARY

The work with regard to establishing the cause of calculus formation has only begun, and all one can hope to do is to arouse interest in a field of research which has received little attention for a number of years. However, the preceding studies have suggested several ideas which seem consistent with clinical and experimental facts.

A Protective Mechanism Against Stone Formation.—Why are not stones formed in the urinary tract of all animals? The human being puts out, on an average, from 2 to 4 gm. daily of material which yields precipitates practically insoluble in water. What prevents the water-insoluble materials from being precipitated and becoming encrusted on the walls of the urinary tract, or clogging it with concretions, just as pipes carrying lime water become covered with calcium carbonate scale? Obviously, nature has provided a defensive mechanism against such deposits in animal excretory organs, more particularly in the urinary tract.

1. *Natural Defense Against Excessive Concentration of Urinary Crystalloids.*—Clinically and experimentally, it has been found that overconcentration of normal urinary crystalloids by dietary means is practically unknown. It is probably impossible. Nature has provided this defense against excessive crystalline deposition in the urinary tract as our first line of defense against stone production.

2. *Protective Colloids.*—The ability of the urine to hold in solution a moderate quantity of material which is practically insoluble in water constitutes a second line of defense against calculus formation. This property of the urine is related to the hydrogen ion concentration and to the presence of protective colloids, as emphasized by Lichtwitz.[11]

3. *Precipitation of Crystals as Isolated Units.*—The third factor of stone prevention lies in the ability of the urine, when it becomes supersaturated, to deposit its crystalline material in isolated, morphologically complete, crystal units which have no tendency to fuse.

4. *The Form and Activity of the Urinary Tract.*—The fourth natural protection against the formation of stone may be found in the anatomy of the urinary tract. The calices lead to the pelvis with open, unobstructed orifices; the pelvis is funnel-shaped and actively contractile, as are also the ureter and bladder, all tending to push any foreign body forward with the urine. It is remarkable that so early a writer as Aretaeus [12] was familiar with this natural defense, for he says, "Nature, therefore, did well in forming the cavity of the kidneys oblong, and of equal size with the ureters, and even a little larger so that if a stone formed above, it might have ready passage to the bladder." So if, in spite of our first three mechanisms, namely, the metabolic protection against excessive concentration of urinary crystalloids, the protective colloids, and isolation of crystals, we should have a formation of small deposits of fused crystals, then this fourth active extruding factor would come into play. This idea is borne out by the frequent passage of small multiple stones and sand which is often seen in patients.

The biliary tract, in this connection, is not such an open system. The inactivity of its contractions, its sinuses of Luschka, valves of Heister, tortuous cystic duct, ampulla of Vater, and sphincter of Oddi, all offer obstruction to the extrusion of crystalline deposits. This may be a significant factor in explaining the greater frequency of gallstones than of urinary concretions.

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11. Lichtwitz, L.: Untersuchungen ueber Kolloide im Urin. II. Ueber Beziehungen der Kolloide zur Loeslichkeit der Harnsaeure und harnsauren Salze, Ztschr. f. physiol. Chem. **64**:144-157, 1910; Lichtwitz, L., and Rosenbach, O.: Untersuchungen ueber Kolloide im Urin. I. Ueber Kolloide im normalen menschlichen Urin, ibid. **61**:112-118, 1909.

12. Adams, F.: The Extant Works of Aretaeus, the Cappadocian, London, Syndenham Soc., 1856, pp. 340-343.

Except in the case of xanthin and cystin calculi, no metabolic error has ever been demonstrated to be associated consistently with lithiasis. In gout, oxaluria, and phosphaturia, our natural defenses against stone formation are actively at work. As a result, stone is the exception in such cases and not the rule.

Cystinuria and xanthuria present unusual crystals in the urinary stream. Their similarity to our artificial oxamiduria in this respect is noteworthy. Here again it may be conceived that the urinary colloids and precipitating mechanism are inadequate properly to handle cystin and xanthin, and a tendency to the formation of stone is the result.

Calculi Due to Abnormal Colloidal Matter in Urine.—There seems to be no other reasonable explanation than that the formation of calculi is due to a disturbance of the normal colloidal mechanism of the urine, either in holding water-insoluble materials in solution or in precipitating crystals as isolated entities. This disturbance may be due to quantitative or qualitative change in the colloids normally present, or to the entrance of abnormal colloids to the urine, either from the blood stream or as products of local disease in the kidney. The latter origin seems most likely.

Specific Exudates from Specific Infection, the Source of Stone-Forming Colloids.—The fact that pus and exudates of bacterial origin, aside from nephritis, are the most common known sources of pathologic colloidal material in the urine makes it seem likely that these constitute the factors by which the normal urinary precipitation mechanism is most frequently upset.

Inflammatory exudates contain albumin, nucleoprotein, lecithin, fatty acids, and other colloids which are foreign to the urinary tract. In consequence of the presence of these pathologic colloids, crystalline material is deposited abnormally. The crystalline material is combined with the organic colloidal material, and when deposited assumes atypical shape and physical structure. Furthermore, these crystals no longer remain isolated but tend to fuse. These fused bodies are for the most part passed on with the urine, but some are retained. Other crystals soon become deposited on the retained mass, and thus a concrement arises.

One point should be emphasized. Not every abnormal colloid introduced into the urinary stream will be associated with atypical crystalline deposits or stone. Were this the case, nephritis and pyelitis would consistently be associated with stone. This leads us again to but one conclusion. The stone forming colloid must be specific, and if due to bacteria the bacteria which produce it must be specific.

Thus we go back to the doctrine of Meckel von Hemsbach who, in 1856, conceived of a "stone-forming catarrh." The demonstration of the elective action of bacteria in different diseases and especially in those

of the kidney, the experimental production of gallstones, of alkaline phosphatic cystitis, and within the last few months, of renal concretions by the methods of Rosenow,[13] almost add the final word to this idea of concrement formation.

Possibility That Calculi Are Occasionally Due to Noninfectious Colloidal Changes.—In spite of the abundant evidence for a bacterial etiology of stone, it is possible that some calculi are not due to infection. Urinary crystalloids may be excreted in such excessive amounts that the normal urinary colloids cannot handle the burden and keep the individual crystals isolated.

On the other hand, qualitative or quantitative changes in the urinary colloids may sometimes be brought about by causes other than bacterial infection. Such changes might rarely lead to the deposition of fusing crystals and consequent formation of stone even though the urinary crystalloid excretion remains within normal limits.

The Rôle of the Mechanical Factors.—In stasis, surface duplication, organic nuclei, and diverticula are seen conditions which do not cause stone but which, if the cause of stone is present, will greatly favor its growth. This has been demonstrated to be the rôle of mechanical factors in the case of oxamid, and all clinical evidence supports such a view for calculi in human beings.

Clinical Application.—The clinical application of this conception of calculus formation strengthens the experimental data. The stone-forming kidney becomes easily understood. The infected kidney pours abnormal colloids into the urine. These cause constant precipitation of crystalloids and fusion of the crystals precipitated. It may be seen readily why the removal of such a kidney is so seldom attended by recurrence of stone; why the recurrence of stone in the infected bladder is so frequent; why bad teeth and tonsillitis, conditions of lowered nutrition, states of inactivity, alcohol or carbohydrate fermentation in the stomach, and other conditions of lowered bodily resistance are accused by various authors of playing a part in the process of lithiasis.

Difficulty is encountered when an attempt is made to explain the high incidence of stone in persons living in India and China, the association of uric acid gravel and uric acid infarcts in children, the alleged association of stone with previous injuries to the vertebral column and spinal cord, and other similar more obscure features of lithiasis. A tentative explanation is the fact that certain physical, climatic, geographic or physiologic differences at times lower the resistance to stone-forming infections.

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13. Rosenow, E. C., and Meisser, J. G.: Nephritis and Urinary Calculi After Production of Chronic Foci of Infection: Preliminary Report, J. A. M. A. **78**:266-267 (Jan. 28), 1922.

Attention should be called also to the occasional instances of spontaneous disintegration of calculi. Englisch [14] collected more than 100 such cases which he considered authentic and a number of others which were questionable. This phenomenon has been explained as due to a resolution of the organic framework, or matrix, of the stone. Rosenbach showed that the kidney stones of man placed in the renal pelvis of animals diminished in size. This suggests that solution of the organic matrix may take place under unusual circumstances.

CONCLUSIONS

The biochemist and physiochemist must lead in the study of the complexities of action of urinary solvents and the states of materials held in solution. As yet, knowledge of the urinary colloids and pigments is very slight, in a true physiochemical sense. In trying to deal with problems of this kind one immediately finds the borderline of scientific knowledge.

On the clinical side, an endeavor must be made to learn what type of bacteria is associated with the process, and whether or not there are specific strains for each chemical in the calculus-forming group. It must be decided why one patient has an oxalate and another a urate or phosphate calculus; why one has a single small stone for years, while another passes many of such size, and why still another presents himself with both kidneys filled with branching stones and without a history of ever having passed sand.

These are the broader aspects of the problem of urinary lithiasis. It is fair to assume, however, that a proper cooperation of biochemists, bacteriologists, and urologists will clear up these points ultimately and bring the problem to a satisfactory solution.

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14. Englisch, J. E.: Ueber spontane Zertrümmerung der Harsteine in der Blase, Arch. f. klin. Chir. **76**:961-1056, 1905.

THE NATURE OF CRANIAL HYPEROSTOSIS OVERLYING ENDOTHELIOMA OF THE MENINGES

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CHICAGO

Local changes in the skull overlying meningeal endotheliomas occur sufficiently often to make their recognition a point of considerable value in distinguishing between endotheliomas and other brain tumors. The changes are of two types, localized bony thickening and local erosion.

LOCALIZED BONY THICKENING

Much the commoner change is localized bony thickening. Cushing [1] found that it was present in some degree in at least 25 per cent. of his eighty cases of meningeal endothelioma. Inasmuch as the proportion of endotheliomas to gliomas is between one to two and one to four (seventy-five meningeal tumors to 142 gliomas in Tooth's [2] series, and eighty endotheliomas to 312 gliomas in Cushing's series), the detection of the hyperostosis would be of value in distinguishing between these two main groups of tumors in one out of every eight to sixteen cases.

Virchow,[3] in 1864, stated that he had several times noticed thickening of the skull overlying endothelioma of the dura. Féré and Arnould,[4] in 1887, reported a case, with symptoms of brain tumor of six years' duration, and a bony thickening of the frontal region for eight months. At necropsy the hyperostosis was found to lie over an egg-sized "angiolithic sarcoma," attached to the inner surface of the dura and projecting into the frontal lobe.

The usual interpretation has been that the growth of the underlying tumor stimulated the overlying bone, leading to nontumorous new bone formation, without recognition of the fact that the bone becomes infiltrated by tumor. This has been the explanation given particularly by German writers, as Krause [5] and Küttner.[6] Early

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1. Cushing, Harvey: The Cranial Hyperostoses Produced by Meningeal Endotheliomas, Arch. Neurol. & Psychiat. **8**:139 (Aug.) 1922.

2. Tooth, H. H.: Some Observations on the Growth and Survival Period of Intracranial Tumours Based on the Records of Five Hundred Cases, with Special Reference to the Pathology of the Gliomata, Brain **35**:61 (Nov.) 1912.

3. Virchow: Die krankhaften Geschwuelste **2**:115, 1864-1865.

4. Féré, C., and Arnould, E.: Compt. rend. Soc. de biol. **4**:220, 1887.

5. Krause, F.: Die allgemeine Chirurgie der Gehirnkrankheiten, Stuttgart, 1914.

6. Küttner, H.: Handbuch der praktischen Chirurgie, Stuttgart, Enke **1**:410, 1921.

reports of microscopic examination of the involved bone are rare. Brissaud and Lereboullet,[7] in 1903, reported two cases which they considered hemicraniosis, i. e., a growth disturbance, associated with angiolithic sarcoma of the dura; but no microscopic examination was made of the bone. They assumed that the dura mater during youth, in its osteogenic capacity, produced the progressive hyperostosis of the skull; when the growth period was finished, its activity was turned in another direction and led to the formation of the intrameningeal tumor. Parhon and Nadjede,[8] in 1905, reported a similar case and gave an abstract of one by Parhon and Goldstein. They considered the bony thickening to be of a tumorous nature; but they gave no details as to its microscopic appearance. Babes, in a discussion as to the relationship between the two tumors, considered them to be of a different nature. He thought that the bony tumor was primary and, by irritation of the meninges, had led to the formation of the intradural psammoma.

Barling and Leith's [9] case, in 1906, was the first published in which it was shown by histologic examination that cells of the same nature as those contained in the intracranial tumor were present throughout the hyperostosis. They considered that the tumor was primary in the meninges, with secondary invasion of the bone by direct extension. No mention is made of the character of the new bone, and it is not stated whether it is believed to come from the tumor or from the invaded skull.

Spiller,[10] in 1907, reported two cases of tumor of the dura mater, with thickening of the overlying bone. He was the first to point out the fact that any pronounced local thickening of the skull is likely to be associated with a tumor involving the underlying meninges. No pathologic report was given of the thickened bone, and it was not stated whether he considered the thickening a hemicraniosis as it was considered by Brissaud and Lereboullet, or due to tumor invasion, as found by Barling and Leith, whose case he cited. From a review of the literature, it appears that the thickened skull has many times been mistaken for the primary tumor and considered as sarcoma, osteoma or exostosis. I have recently seen two cases in which the disease had been considered sarcoma of the skull. In such cases, the intradural lesion has been either overlooked or considered secondary, from direct extension through the dura.

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7. Brissaud and Lereboullet, P.: Rev. neurol. **11**:539 (June) 1903.
8. Parhon, C., and Nadjede, G.: Rev. neurol. **13**:1017 (Nov.) 1905.
9. Barling, H. G., and Leith, R. F. C.: Lancet **84**:282 (Aug. 6) 1906.
10. Spiller, W. G.: Hemicraniosis and Cure of Brain Tumors by Operation, J. A. M. A. **49**:2059 (Dec. 21) 1907.

Cushing's recent report of the first extensive series studied by a single observer contains much general information on the subject, especially as to the frequency of occurrence and the localization of the hyperostoses and the types of intradural lesions producing them. Tumors of the frontal and temporal regions, and particularly those whose origin is near the falx, were found to produce bony thickening most frequently. The primary intradural tumor was of two types, either spherical and embedded in the brain substance, with a variable extent of attachment to the dura, or endothelioma en plaque, with a broad attachment to the dura, and producing only slight indentation of the brain surface. The latter was much more inclined to produce hyperostosis than the former, and the hyperostosis was likely to be larger, the exact reasons for which were not clear. That the degree of hyperostosis was not definitely related to the extent of dural attachment was shown by cases in which rounded tumors with small dural attachments caused marked bony thickening. Cushing found endotheliomatous invasion of the thickened bone in all cases in which it was examined, and he considered the thickening to be due to the stimulating effect of the invading tumor, although he thought it possible that the ossification might be of the tumor and in some way connected with the osteogenetic power of the dura.

REPORT OF CASES

As yet there have been few detailed studies published of both gross and microscopic features of the thickened bone and of its relation to the underlying dura. The two cases reported herewith have afforded opportunity for such study, and throw some light upon these points.

CASE 1.—R. M., man, aged 40, entered the Presbyterian Hospital in March, 1915, on the service of Dr. Bassoe, giving a history of headaches during the last two years, which had gradually increased in severity and frequency. For six weeks, there had been failing vision and attacks of vomiting. The examination showed greatly reduced vision and bilateral choked disk. It was otherwise negative, there being no focal symptoms of brain tumor. A roentgenogram was taken; but the findings were not recorded, and the plate was subsequently lost. A subtemporal decompression was performed by Dr. Bevan, and ten months later, because of recurrence of symptoms of intracranial pressure, the cerebellar region was explored, but no tumor was found. Death occurred eleven months after admission.

At necropsy, after reflection of the scalp, a diffuse hyperostosis was noted in the right occipital region. On removal of the skullcap, a crater-like depression was found in the right occipital lobe, produced by an internal bony thickening similar to and opposite that on the outside and markedly adherent to the dura. A large spherical tumor was deeply embedded in the underlying occipital lobe and adherent to the overlying dura at the tip of the depression (Fig. 1).

Bassoe[11] has published a pathologic report of the tumor. It was an endothelioma with numerous whorls, but with complete absence of either calcification or ossification. The dura in the region of the tumor and hyperostosis was well preserved, and its vascular markings could be made out. At the pit of the crater into which the hyperostosis fitted, there was a small perforation. The tumor was spread out laterally and anteriorly for several centimeters in a thin layer between the dura and brain substance. Microscopic

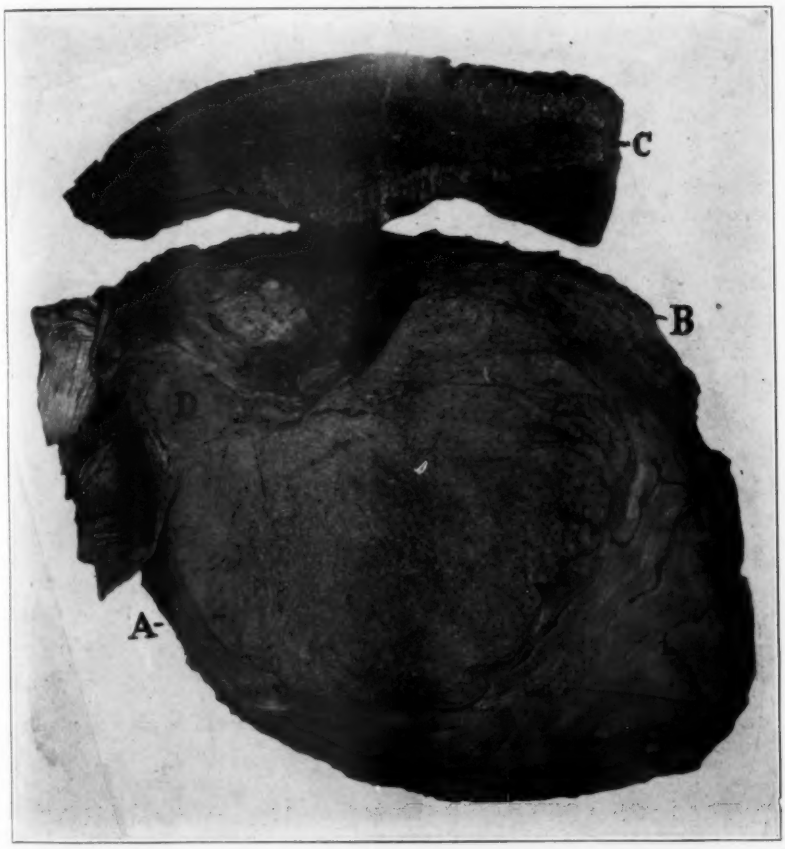

Fig. 1 (Case 1).—Coronal section through right occipital lobe and overlying thickened skull; dura removed from lateral portion of depression and lateral cortex: (*a*) tumor mass dipping into brain; (*b*) thin layer of tumor spread over lateral cortex of lobe; (*c*) outline of old calvarium, and (*d*) tumor filling superior longitudinal sinus.

examination of the dura, excised near the apex of the depression, showed extensive tumor infiltration with marked dilatation of some of its vascular spaces and tumor invasion of others. Sections of the dura overlying the

11. Bassoe, Peter: Two Cases of Tumor of the Occipital Lobe, Tr. Chicago Path. Soc., 1917, p. 118.

Fig. 2 (Case 1).—Roentgenogram of section, showing spongy character of hyperostosis and of invaded calvarium as compared with the denser uninvolved portion (*a*).

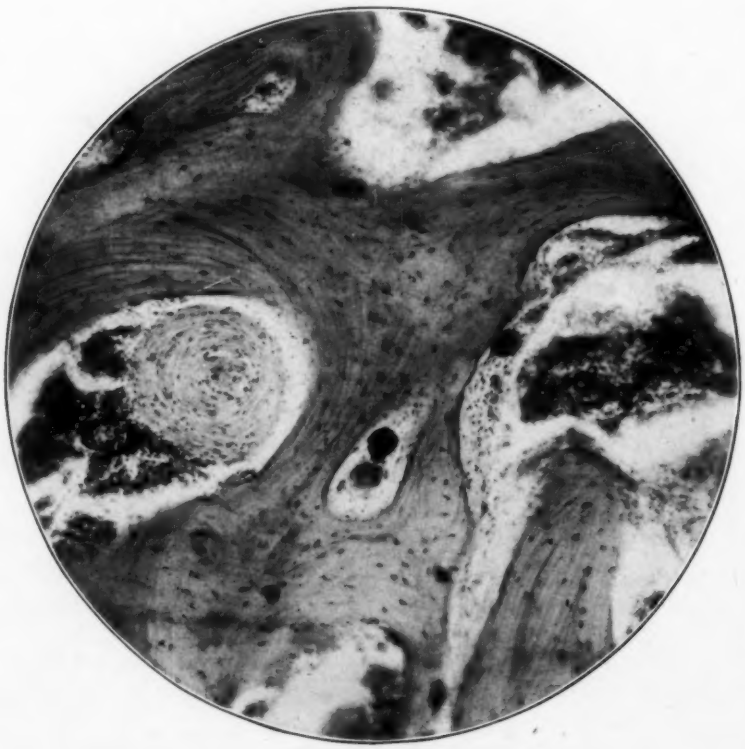

Fig. 3 (Case 1).—Endothelioma infiltrating calvarium.

thin layer of the tumor spread out between it and the cerebral cortex showed very little invasion by tumor cells.

Section through the middle of the overlying thickened bone revealed clearly the outline of the old calvarium. The zone of hyperostosis averaged 7 cm. in diameter and gradually tapered off toward the periphery. The thickening was slightly greater on the outside than on the inside. The skull measured 2.6 cm. in its thickest portion. The new bone was, in general, spongy; but in places it had a slight tendency to radiate from the outer and inner tables. The calvarium was definitely more spongy in the region of the hyperostosis than in its uninvolved portion. The inner surface of the hyperostosis was quite rough and showed many grooves and canals, some of which were vascular markings. The outer surface was covered by smooth pericranium. A roentgenogram of an excised narrow strip revealed the spongy character of the hyperostosis and the reduced density of the outer and inner tables, as compared with the uninvolved skull at one end of the section (Fig. 2).

Fig. 4 (Case 2).—Appearance of patient on examination.

Microscopic examination showed endothelioma of the same character as the intradural tumor, infiltrating almost uniformly the entire hyperostosis and the portion of the skull from which it sprang (Fig. 3). The cancellous spaces were largely filled with tumor and blood vessels, red marrow being extremely scanty. New bone was being formed about the surface of the external layer, and its nontumorous nature could be definitely made out. In the regions of most marked growth, tumor cells were largely absent in the vicinity of the newly formed trabeculae, and bone formation from tumor cells was nowhere to be seen. Fibrous bands dipped into the substance of the exostosis at irregular intervals, especially about the pericranial surface, dividing it into radiating columns. Along the endosteal surface, tumor was especially abundant and extended into the slight remnants of dura which were adherent to the hyperostosis in a few places.

Case 2.—A. H., man, aged 31, was admitted, Aug. 15, 1922, to U. S. Veterans' Bureau Hospital No. 76. During the previous two years, a hard, bony, oval swelling had gradually developed in the left frontoparietal region. There were

no other symptoms. Examination revealed a large, oval, bony, hard, painless swelling in the left frontoparietal region, extending forward almost to the orbit, backward as far as the plane of the posterior part of the auricle, and mesially just beyond the midline of the skull (Fig. 4). There were no other positive findings. The nervous system and eye-grounds were negative. A roentgenogram showed a shadow in the region of the tumor, gradually increasing in density toward its central portion. The new bone, extending beyond the outline of the outer table, cast a faint, but definitely radiating, shadow (Fig. 5). A probable diagnosis was made of meningeal endothelioma, with overlying hyperostosis.

Operation was performed in two stages, ten days apart. A large flap was turned forward and to the left; and five trephined openings were made about

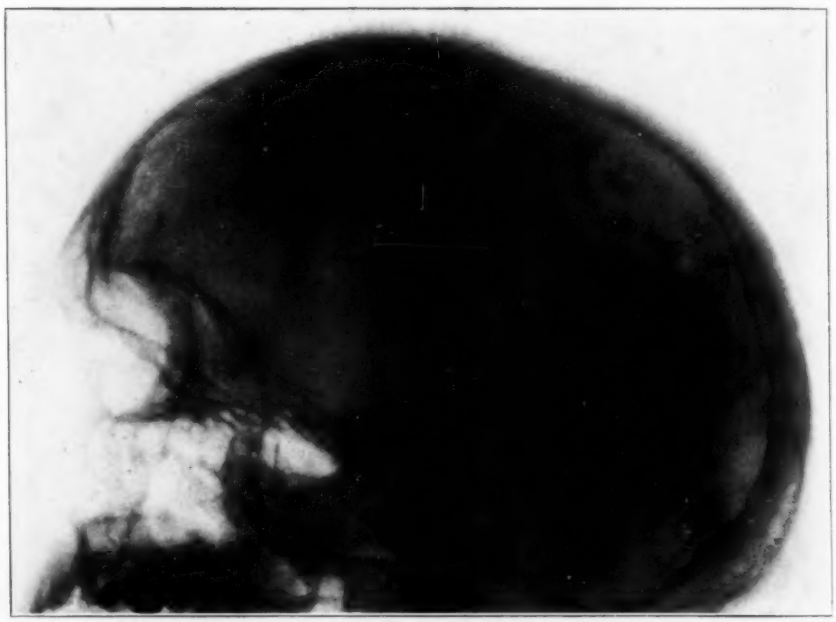

Fig. 5 (Case 2).—Roentgenographic appearance of head.

the periphery of the tumor. All except one of the intervening bridges were cut, and the wound was closed. Ten days later, the wound was reopened, the remaining bridge cut and the thickened skull removed. It was markedly adherent by its inner surface, and, in one place, the outer layer of dura was removed with it. The exposed dura was then opened, and a broad, flat tumor was found attached to its inner surface. The involved dura was excised at a distance of about 1 cm. from the margin of the tumor, except near the superior longitudinal sinus, where the tumor extended to the margin of the falx and small fragments on its external surface were left behind. These were curetted off as well as possible. Three large cerebral veins extending from the cortex in the Rolandic region to the involved dura were ligated. The wound was closed without repairing the cranial defect. Right hemiplegia and

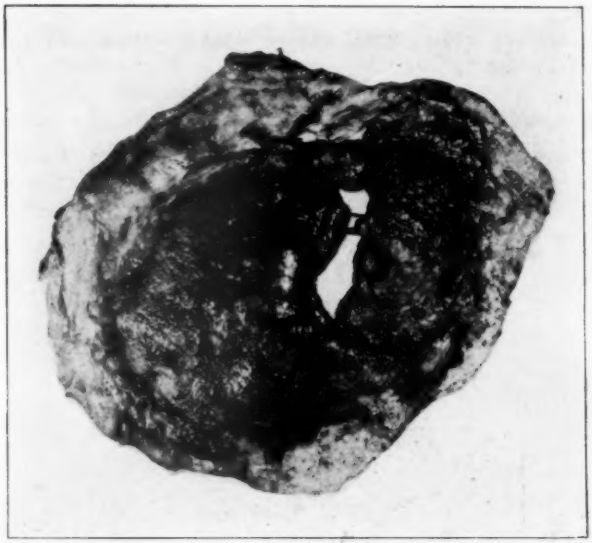

Fig. 6 (Case 2).—Inner surface of excised dura, showing attached flat tumor.

Fig. 7 (Case 2).—Section of tumor.

motor aphasia followed the operation. Three months later, both the hemiplegia and the speech disturbance were rapidly improving.

Pathologic Report.—The excised dura presented on its inner surface, a flat, oval tumor, 8 cm. long, 5 cm. wide and 1.5 cm. thick, at its central portion (Fig. 6). The tumor was grayish red, soft and friable. It tapered off gradually at the periphery. The outer surface of the dura, which was firmly adherent to the overlying bone, had a ragged appearance and was grayish red in places from tumor infiltration. Microscopic examination showed the tumor to be composed very largely of endothelial cells which had only a slight tendency to arrangement in whorls. Evidences of cell division were

Fig. 8 (Case 2).—Excised hyperostosis sawn in two, showing external, cut and internal surfaces with attached fragment of dura (*a*).

not seen. There was little fibrous stroma, and blood vessels were numerous. There was no evidence of hyaline degeneration or calcification (Fig. 7). Sections through its attachment showed the dura extensively infiltrated with tumor; but in no place had the dural membrane been completely destroyed and replaced by tumor.

The excised portion of the skull (Fig. 8) showed extensive oval bony thickening, which was more marked on the outside than on the inside. The inner surface was rough and bare, except in its lateral portion, where there was still attached a dollar-sized piece of the outer layers of dura, extensively infiltrated with tumor. The outer surface was smooth and covered by thickened pericranium with portions of attached temporal muscle. A cross-

section showed the outline of the old calvarium, with a layer of new bone radiating from either surface. The maximum thickness of the skull was 4 cm.; the external layer measured 2 cm., and the internal layer, 1.2 cm. The density of the outer layer was quite uniform; but that of the inner layer was more variable. In its lateral portion, which was covered by a dural fragment, there was only a small amount of ossification, and numerous radiating fibrous bands originating from bone attached the dura to the inner table. Calvarium from which the hyperostosis sprang was grayish red, and the tables were slightly porous, as compared with uninvolved portions at the periphery. A section, 0.5 cm. thick, was excised for further study. A roentgenogram of it (Fig. 9) showed the arrangement of the old and new bone in detail. The inner and outer tables were slightly more spongy than normal. The new bone, both internally and externally, radiated from the surface of the old bone. The rays were coarser and more uneven on the inside than on the outside. The inner layer showed plainly that ossification had proceeded from the

Fig. 9 (Case 2).—Roentgenogram of excised strip, showing hyperostosis radiating from the inner and outer tables and the reduced density of invaded calvarium.

inner table toward the dura and not in the opposite direction, as should be the case if the new bone were formed from the tumor. Sections including the entire thickness of the skull were cut in four places for microscopic examination. They showed a variable amount of tumor infiltration of the calvarium and of the new bone springing from it. The tumor was of the same character as the primary growth. The inner layer of new bone was extensively infiltrated (Fig. 10); but there were numerous areas, especially in its denser portions, which contained little tumor. The inner and outer tables were more porous than normal, and there was considerable tumorous infiltration of them as well as of the diploë. The external hyperostosis contained the least amount of tumor. Its deeper and peripheral portions were considerably infiltrated; but the superficial bone in the thicker portions was almost entirely free from tumor (Fig. 11). There were marked degenerative changes in the deeper areas, the result of circulatory disturbance produced by the first operation. Coarse bony trabeculae sprang from the tables at right angles to their surfaces, and many of them showed evidences of new bone formation at their

tips. In some regions, tumor almost completely filled the cancellous intercolumnar spaces. In others it was mixed with fibrous bone marrow. The new bone, which was free from tumor, contained a richly cellular fibrous and hemopoietic marrow. There was no question that the new bone was not tumor, for in many places along the surface where it was in the process of formation, several adjacent low power fields failed to reveal a tumor cell. A section through the region of attached dura disclosed that it was extensively infiltrated with tumor. Much of this ran parallel to the dural fibers; but in places tumor

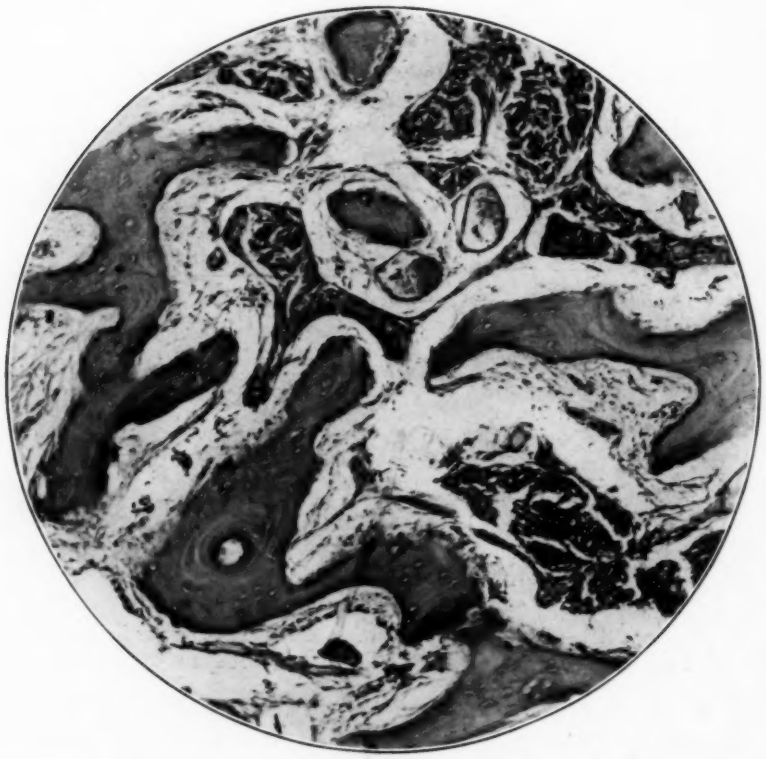

Fig. 10 (Case 2).—Internal hyperostosis with much tumor in the cancellous spaces.

bands broke through the membrane and ran at right angles to the overlying new bone. No large vascular channels were seen to pass from dura to skull, along which the tumor had spread. While the hyperostosis was much more marked in this case than in Case 1, the tumor infiltration of the new bone was very much less marked and less uniform in distribution.

COMMENT

The findings in these two cases suggest the following order of development of pathologic changes: The primary tumor arises inside the dura from cells connected either with its inner lining or with the

arachnoidal villi which project into the dura, as held by M. B. Schmidt [12] and Cushing and Weed.[13] As the tumor grows, its cells penetrate the dura and invade the overlying bone, throughout which they spread. Instead of eroding the skull, the tumor exerts a stimulating influence upon it. The result is the formation of a hyperostosis, which consists of two intermixed portions, namely endothelial tumor and a newly formed, nontumorous bony framework. The proportions of each vary

Fig. 11 (Case 2).—Section of proliferating surface of external hyperostosis showing nontumorous new bone formation and only one island (*a*) of tumor; (*b*) pericranium.

in different hyperostoses and in different portions of the same hyperostosis, as shown by comparison of the findings in these two cases. That the new bone does not originate from tumor cells is substantiated by a number of facts. In the first place, the intrameningeal portion

12. Schmidt, M. B.: Arch. f. path. Anat. u. Physiol. **170**:429, 1902.

13. Cushing, Harvey, and Weed, L. H.: Studies of the Cerebrospinal Fluid and Its Pathway: IX. Calcareous and Osseous Deposits in the Arachnoidea, Bull. Johns Hopkins Hosp. **26**:367 (Nov.) 1915.

of the tumor does not ossify, at least to any appreciable extent. If its cells were osteogenetic, there should be ossification of the intradural as well as of the extradural portion. The arrangement of the new bone suggests that its origin is from the skull instead of from the tumor. It grows out of, and, to a variable extent, radiates from, the old bone. Microscopically, the new bone is seen to form from normal osteoblasts and not from tumor cells.

Fig. 12.—Segment of femur infiltrated with osteoplastic metastases from carcinoma of prostate; new bone in the surface nodules has finely radiating arrangement.

The reasons for this invasion of the bone and for its osteoplastic response are not well understood. Endotheliomas behave as do benign tumors in their method of spread, which is always by direct invasion of surrounding tissue and never by metastasis. However, in this deeply penetrating infiltration of bone, they resemble malignant tumors. Also their tendency to invade the dura and grow for long distances in

its vascular channels is well known. In Case 1 the adjacent portion of the superior longitudinal sinus was completely filled with tumor, and the growth extended as far back in it as the torcular herophili. With regional blocking of the normal venous channels of the dura from tumor invasion, there may be a compensatory increase and dilatation of vascular connections with the overlying bone, facilitating tumor infiltration. Spread of the tumor into the bone may be favored in this way, in the absence of increased intracranial pressure which would tend to drive blood and tumor toward the periphery.

The hyperostosis is then an instance of osteoplastic invasion of bone by a mesoblastic tumor originating outside the skeleton. Invasions of bone by all other nonbony mesoblastic tumors, whether by direct extension or through the blood stream, are osteoclastic, that is, they destroy bone, and there is no new bone formation throughout their substance. Analogous changes are produced by carcinomatous invasion of bone. Usually, carcinoma metastases are osteoclastic; but, in certain instances, notably when from carcinoma of the prostate, they may stimulate new bone formation, and ossification occurs throughout the substance of the metastases. The medullary cavity of a long bone or the cancellous spaces of a short one, as a vertebra, may be completely filled with new bone formed as the result of stimulation by such metastases, and carcinomatous nodules springing from the surface of such a bone may possess an ossified stroma with slight radiations, similar to that in the hyperostosis shown in Case 2. In Figure 12 is reproduced a roentgenogram of a postmortem specimen of a femur, with ossified metastases both in the medullary canal and along the surface of the cortex, secondary to carcinoma of the prostate. The new bone is, of course, formed from the old and not from carcinoma cells, and fine radiations are to be seen in the peripheral portions. These were best seen on microscopic examination. Von Recklinghausen [14] explained the new bone formation in ossifying carcinoma metastases in the following way: The tumor growth lies almost entirely within the veins and obstructs them, producing marked passive hyperemia of the region. This stimulates the new bone formation. Axhausen [15] and Schmorl [16] believe that the new bone forms as a result of stimulation by chemical substances liberated by the tumor cells. One type of tumor cell stimulates stroma formation, while another does not, and, when the tumor growth is within a bone, the stroma arises from it and ossifies. There is uncertainty as to the relationship between the amount of fibrous stroma contained within the intradural endothelioma

14. Von Recklinghausen, F. D.: Festschr. Rudolf Virchow, Berlin, 1891.
15. Axhausen, G.: Arch. f. path. Anat. u. Physiol. **195**:358, 1909.
16. Schmorl: Verhaudl. d. deutsch. path. Gesellsch. **12**:89, 1908.

and the amount of ossification within the tumor invading the skull. In Case 2 stroma was very small in amount in the intradural portion, and ossification of the skull invasion was very marked. While in the endotheliomatous hyperostoses the larger venous channels of the overlying dura and skull may show tumorous invasion, the smaller veins and capillaries are not uniformly engorged with tumor cells, as is the case within ossifying carcinoma metastases.

The arrangement of new bone within an ossifying bony tumor, whether the tumor is primary or secondary, seems to be dependent more on its amount and rate of formation than on the nature of the cells from which it springs. Whether it arises from tumor cells or from the old bone, it is arranged to support the tumor. If the growth of the tumor is fairly rapid or if the amount of bone formed throughout its substance is not very great, the newly formed bone is likely to radiate from the surface of the old. This is commonly seen in periosteal sarcomas in which the new bone is tumorous. If the rate of growth is slow or the tendency to ossification great, the newly formed bone is likely to have a dense, spongy arrangement. Combinations of the two are not infrequently seen, the deeper bone being dense and spongy, while superficial portions show radiation.

Opposed to the theory that the endothelioma cells ossify as a result of osteogenetic powers contributed by the dura are not only the histologic findings, but also the fact that a tumor arising from the dural infoldings, which contain no osteoblastic layer, may produce hyperostosis. Heuer and Dandy[17] reported a tumor apparently springing from the falx, which extended to the surface in the lateral portion of the frontal lobe and produced bony thickening of the overlying skull. Calcification occurring in areas of hyaline degeneration in psammomas is, of course, in no way related to the bony thickening of the skull.

Primary tumors of the skull may resemble very closely these hyperostoses secondary to meningeal endotheliomas. This is particularly true of those lesions which begin early in life, grow slowly and are regarded either as benign tumors or as hyperostoses cranii. After many years of comparatively innocent growth, they may take on definite sarcomatous features. Such was the case in the remarkable bony growth, apparently primary in the left frontal bone, in the giant Wilkins, reported by Bassoe.[18] The patient began to grow abnormally rapidly at the age of 4, and by his eighteenth year he had attained the height of 8 feet 2 inches (249 cm.). At the age of 8 a slight thickening of the frontal bone developed, just above the left orbit. This continued to grow slowly for twenty years, at the end of which time a large bony tumor

17. Heuer, G. J., and Dandy, W. E.: A Report of Seventy Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**:224 (Aug.) 1916.

18. Bassoe, Peter: J. Nerv. & Ment. Dis. **30**:513, 1903.

mass had formed, involving most of the frontal bone, distorting the face and extending into the left temporal region. A second and apparently independent bony thickening formed at the temporoparietal junction, just above the left mastoid. Three months before death at the age of 28, the tumor began to increase rapidly in size and became painful. Vision was rapidly lost and symptoms of increased intracranial pressure appeared. At necropsy the tumor was found to lie entirely outside the dura. It had greatly encroached upon the left frontal and temporal lobes at the base of the brain. There was enormous bony thickening of the skull, which was mainly on the outer surface of the involved region. There was a large soft tumor between the dura and inner portion of the bony growth, which had nowhere penetrated the dura. Microscopic examination revealed a round-cell and spindle-cell sarcoma, ossifying in its outer portion. The dense peripheral portion contained much mature bone which bore considerable resemblance to an ordinary hyperostosis.

Since it has recently been demonstrated, especially by Ewing,[19] that endothelioma of bone is not uncommonly encountered, these cases should be analyzed from the standpoint of primary endothelioma of the skull, with secondary invasion of intracranial structures. This is particularly true of the cases, such as Case 2 of this series, with marked hyperostosis and small, flat, intradural tumor. Primary endothelioma of bone differs strikingly from these cases in that there is nearly always extensive bone destruction, with little or no associated new bone formation. This is true of the few instances, as those of Kocher,[20] Rustitzky,[21] Marckwald[22] and Ewing, in which the skull was the bone involved. I find no recorded case of extension through the dura producing a subdural mass and symptoms of brain pressure. Ewing has reported one case in which there was diffuse, spindle shaped enlargement of the ulna, with spongy ossification throughout the tumor.

LOCAL BONE DESTRUCTION

When a meningeal endothelioma invades the overlying skull, it may produce bony erosion with little associated new bone formation. The skull may be perforated, and the overlying scalp may be lifted up or invaded by the soft tumor. This condition is referred to in the old literature as fungus durae matris. Andrews[23] has recently reported such localized bone destruction from an underlying meningeal tumor.

19. Ewing, James: A Review and Classification of Bone Sarcomas, Arch. Surg. **4**:485 (May) 1922.

20. Kocher: Arch. f. path. Anat. u. Physiol. **44**:311, 1868.

21. Rustitzky: Deutsch. Ztschr. f. Chir. **3**:162, 1873.

22. Marckwald: Arch. f. path. Anat. u. Physiol. **141**:128, 1895.

23. Andrews, E. W.: Surg. Clinics of N. America, 1923, Chicago Number, to be published.

In some instances of tumor invasion of the skull, there forms first a hyperostosis; but, as growth continues, there is gradual erosion from within outward, not only of the newly formed bone, but also of the old bone, so that eventually the unossified portion of tumor may either perforate the skull or be covered by a thin layer of the remaining external bony thickening. Ossification may occur early in the external growth of tumor and then cease, after which a considerable amount of unossified tumor may accumulate on top of the hyperostosis. This combination is well illustrated by Case 3.

Fig. 13 (Case 3).—Endothelioma of twelve years' duration, producing first hyperostosis, then erosion of calvarium from within outward and a layer of unossified tumor external to the hyperostosis.

REPORT OF CASE

Case 3.—A woman, aged 69, for twelve years had had an oval enlargement in the frontoparietal region, centering to the left of the midline. It had slowly increased in size until at the present time it formed a mass larger than the one in Case 2. During the last year there had been disturbances in gait and mental disturbance indicative of cerebral involvement. On palpation, the tumor had a bony feel in its deeper portions; but it was soft in its outer layer. A roentgenogram of the skull (Fig. 13) showed spongy ossification in the deeper portion of the external tumor, but no evidences of new bone formation in its superficial part. There was a crater-like depression at the apex of the bony thickening. There was evidence of erosion of the entire

thickness of the skull from within outward, in the central and posterior portions. A piece of tumor was excised for microscopic examination. There was an unossified external layer, at least 1 cm. thick, which had invaded the scalp. It proved to be a typical endothelioma containing little fibrous stroma.

COMMENT

There has been a tendency for pathologists to classify many of the meningeal tumors with the sarcomas; but, as Cushing has pointed out, they all possess sufficiently peculiar common characteristics, such as failure to make metastases, to be grouped separately and designated as meningotheliomas or meningiomas. Some tumors are composed very largely of spindle cells, as if they originated in the connective tissue element of the dura. The question arises whether the less the endothelial content of the tumor, the less the tendency to bone invasion. I have examined a flat tumor of the dura with the dimensions of that in Case 2, except that it was slightly thicker. The overlying bone was normal in appearance despite the fact that tumor lay in contact with it, and microscopic examination of the bone showed complete absence of tumor invasion. Histologically, the dural tumor was composed almost entirely of spindle cells arranged mainly in irregularly coursing bundles.

These cases illustrate well the extreme variation in effects upon the nervous system of tumors associated with hyperostoses. In the first case, there were typical general symptoms of brain tumor, and the hyperostosis was not sufficiently prominent to attract the attention of the clinician. In the second case, nervous symptoms were entirely absent, and the hyperostosis was the sole complaint. Such cases as the latter have not infrequently been diagnosed as sarcoma or osteoma of the skull and the underlying tumor overlooked. This has happened even when evidences of brain compression were present, as the internal hyperostosis was held responsible for the compression. In cases, as that of Spiller, in which only the thickened skull was excised, the continuation of brain pressure symptoms has led to a second operation, at which the primary intradural tumor was found and removed. A small endothelioma has been known to produce localized hyperostosis from the inner table without the development of either neurologic symptoms or external tumor, and the condition has been discovered only at necropsy (Virchow).

A point of practical importance in dealing with the thickened skull at operation has been emphasized by Cushing, Elsberg,[24] Krause, and others, namely, that it is not essential to remove all of the thickened bone. After removal of the intracranial tumor, there is usually little tendency for the hyperostosis to increase in size, and patients have been

24. Elsberg, C. A., in discussion on Cushing, Harvey: Arch. Neurol. & Psychiat. **8**:139 (Aug.) 1922.

observed to remain well for years when considerable involved bone was left behind. This is additional proof of the benign nature of the tumors. However, the involved bone may continue to enlarge and produce pressure upon the brain or recurrence within the meninges. Frazier (personal communication) operated repeatedly on the patient in Case 2 of Spiller's report, before the fatal termination, several years later. A method of dealing with the defect left after removal of a large hyperostosis, as in Case 2 of the present report, would be to chisel away immediately the bony thickening from the inner and outer tables, boil the remaining calvarium while the intradural operation is being completed, and reinsert it before closure of the scalp.

SUMMARY

The hyperostosis which develops over a considerable proportion of meningeal endotheliomas results from penetration of the dura and direct invasion of the skull by the tumor. The tumor permeates the skull, rarefies slightly the inner and outer tables and stimulates new bone formation, usually from both the internal and external surfaces. Tumor cells are found in varying numbers throughout the cancellous spaces of the hyperostosis. The new bone is not tumorous in nature, and is merely ossified stroma of the invading endothelioma. Its spongy or radiating arrangement is similar to that which is seen in the ossification occurring in other types of tumor, whether primary or secondary in bone and whether the new bone itself is of tumorous or nontumorous nature.

OSTEOMA OF THE SKULL

REPORT OF TWO CASES, ONE BEING ASSOCIATED WITH A LARGE INTRACRANIAL ENDOTHELIOMA

CARL W. RAND, M.D.

LOS ANGELES

As far as I know, no comprehensive treatise on the subject of bony tumors of the skull, and their relationship to underlying endotheliomas, has yet appeared. Sporadic cases of cranial osteoma and hyperostosis, sometimes with, and sometimes without, this associated pathologic condition, have been reported; but these are frequently found under obscure titles. That local thickening of the skull may occur has long been known. It is seen in various systemic conditions, such as acromegaly, Paget's disease, oxycephaly, turricephaly, periosteal inflammatory reactions, etc., as well as in actual tumor formations. In the latter conditions, the thickening may involve the skull alone or may be accompanied by an underlying endothelioma. On the other hand, intracranial endotheliomas probably more often occur without any hyperostosis of the overlying skull. A close relationship between these conditions is becoming more generally recognized, and the surgeon who sees a case presenting a local thickening of the skull is at once suspicious of some underlying tumor.

Spiller [1] in 1907 gave us one of the earliest finished reports of an endothelioma of the brain associated with thickening of the overlying skull. The patient was operated on by Frazier, who first removed an area of thickened bone and later—as the symptoms did not clear up satisfactorily—reopened the wound and removed an endothelioma in the region of Broca's area. On occasion, these growths may be of a more extensive nature. Mix [2] has reported a case in which the growth involved the scalp, skull and underlying brain. Cushing,[3] reporting on hyperostoses of the skull, found the condition to be present in twenty instances in a series of eighty endotheliomas. Of these twenty cases, eight were endotheliomas of the soft, flattened type, and twelve were of the rounded type, having a relatively small meningeal attachment and usually spoken of as enucleable. He believes that at least 25 per cent. of cases of proved endotheliomas present demonstrable thickening of the overlying bone.

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1. Spiller, W. G.: Hemicraniosis and Cure of Brain Tumor by Operation, J. A. M. A. **49**:2059 (Dec. 21) 1907.

2. Mix, C. L.: Endothelioma of the Dura, M. Clinics N. Am. **5**:1673 (May) 1922.

3. Cushing, Harvey: Cranial Hyperostoses Produced by Meningeal Endotheliomas, Arch. Neurol. & Psychiat. **8**:139 (Aug.) 1922.

The pathology of these so-called endotheliomas has been studied by Mallory [4] from the standpoint of cell morphology. He has advanced the theory that they grow from the arachnoid villi rather than from the dural endothelium. In short, he denies the existence of a dural endothelium, stating that the under surface of this membrane is lined with fibroblasts rather than with endothelial cells. In comparing the structure of endotheliomas with a series of arachnoid villi in various stages of proliferation, he seems to show that the so-called dural endothelioma is composed of arachnoid cells and elastic fibrous tissue. He suggests the term "arachnoid fibroblastoma" as being more correct from a morphologic standpoint, and holds the opinion that these growths may invade the overlying bone and scalp but that they never really invade the brain tissue proper, because their blood supply is derived from the dura and not from the nonvascular arachnoid membrane.

The following cases are presented as being representative of types of hyperostosis of the skull; the first accompanied by an underlying endothelioma which filled, and grew from both sides of the longitudinal sinus; the second, a simple osteoma of the skull not associated with any true intracranial growth.

CASE 1.—*History.*—J. A. M., man, aged 31, married, an expert accountant, was referred by Dr. H. G. Brainerd of Los Angeles, Feb. 20, 1920. He had always been athletic, having played football, basket ball, etc., and, although he had been knocked out once or twice, there was no definite single history of severe skull injury at any time.

About January, 1913, his wife first noticed a small, hard, bony lump, about the size of a marble, on the crown of his head, near the juncture of the sagittal and coronal sutures. The patient was not aware of its presence, and had no symptoms of any kind. About February, 1914, following a severe cold, the patient states that the lump was again examined and found to be larger than before. In March, 1914, following exposure to the sun, he had his first convulsion at 4 a. m. About this time, he showed other symptoms, becoming nervous, irritable and somewhat unreliable in his business relations. In July, 1916, the second convulsion occurred; twenty-four days later, the third convulsion occurred, and eighteen days later, the fourth convulsion. The last convulsion was seen by a physician who pronounced it an attack of jacksonian epilepsy. Ten days later, the fifth convulsion occurred, and, Sept. 6, 1916, the patient was operated on at Prescott, Arizona, by Dr. J. B. McNally. A piece of bone was removed from the vertex, measuring 2½ by 2½ inches (6.3 by 6.3 cm.) in diameter, and 1½ inches (3.8 cm) in thickness. The pathologic report of this tumor was: "benign osteoma showing irregular growth of the bone." Dr. McNally writes as follows: "Examination of the skull showed an unusual, large prominence on the frontal bone, slightly to the left of the median line, extending as far back as the coronal suture. I found the bone to be enormously thickened, and, while it was peculiarly smooth on the surface, the section which I removed had projecting from its inner surface several

4. Mallory, F. B.: The Type Cell of the So-Called Dural Endothelioma, J. M. Research **41**:349 (March) 1920.

little bony spicules, sharp pointed, which produced a shredding of the dura so that the dura mater was practically destroyed and the cortical surface was smeared with a wine-colored jelly-like substance, and all membranes at this point appeared to be destroyed. There was no evidence of pus infection. I cleaned out all the débris as gently and as carefully as possible, and controlled the bony oozing with sterile beeswax. I carefully inserted the little finger around the inner aspect of the skull for half an inch or more, but could not detect any roughness on the inner surface. I remember, however, that the anterior horn of the rim was unusually thick."

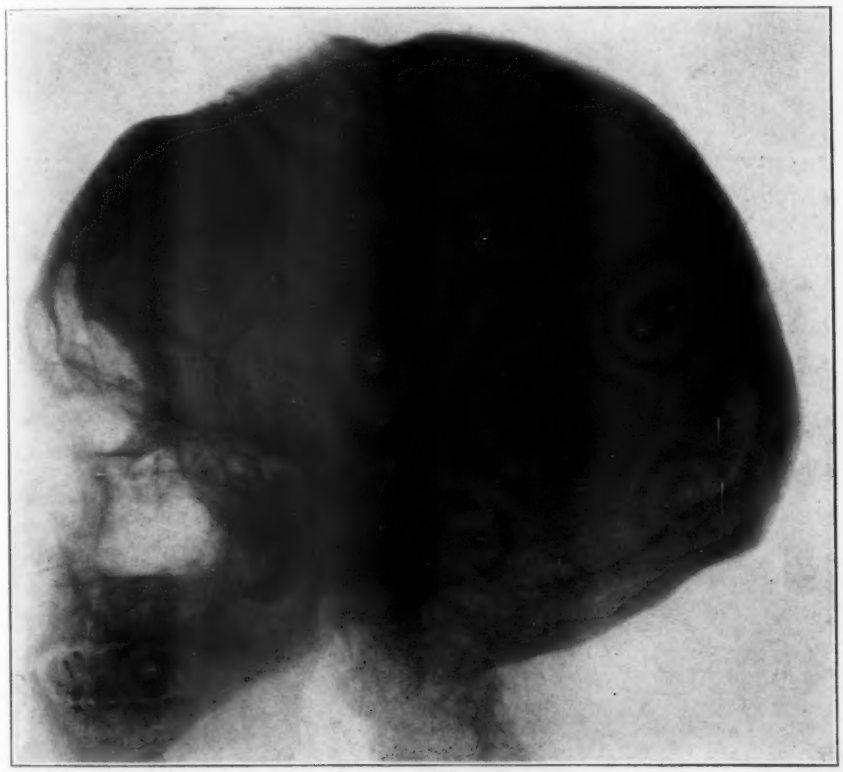

Fig. 1 (Case 1).—Lateral view of skull, showing tremendous thickening of the calvarium at tumor site, 1920. The recurrence of bony growth, following attempted removal four years previously, may be noted.

The patient returned to work Nov. 15, 1916, much improved. Jan. 6, 1917, the sixth convulsion occurred. The seventh occurred on the 24th of March, 1917, following which the patient took several months' rest. The eighth convulsion occurred about August, 1917; the ninth and tenth, five days apart during the middle of September, 1917; the eleventh and twelfth in November, 1917, the thirteenth, Dec. 15, 1917, and the fourteenth, Feb. 15, 1918. Nov. 1, 1918, the patient contracted influenza, which was followed by double pneumonia. He was very ill for several weeks. In January, 1919, the fifteenth

Fig. 2 (Case 1).—Lateral view of bony tumor removed in 1920; weight, 105 gm.

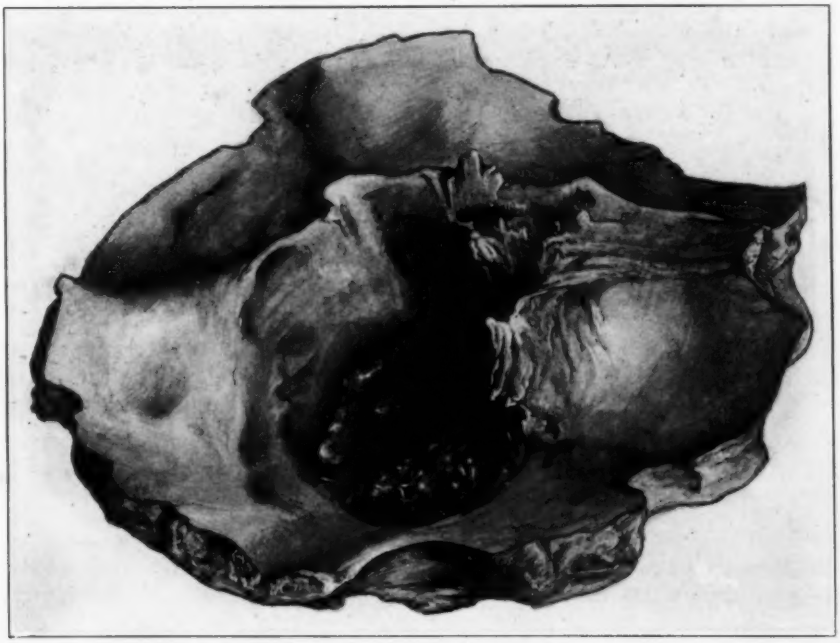

Fig. 3 (Case 1).—Inferior view of bony tumor showing previous operative defect and spicular growth.

convulsion occurred. During this period, the patient was working, being kept on bromids. About this time, he became very irritable, difficult to live with, and got into financial difficulties. At one time, he left home for a week without apparent cause.

Examination.—When he came under observation, Feb. 20, 1920, examination revealed a well-nourished young man, in good general physical condition, who was suffering somewhat from headache. He was very nervous and irritable.

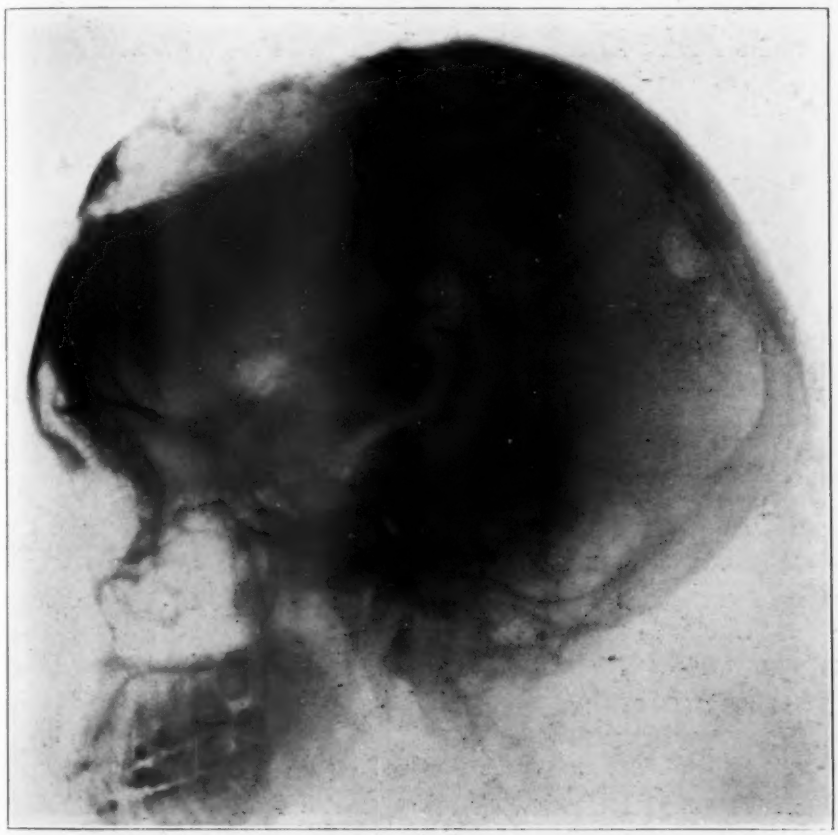

Fig. 4 (Case 1).—Lateral view of skull with patient in supine position. The recurrence of bony growth, also inflation of right lateral ventricle with air showing the anterior horn indented and pushed down by endothelioma, may be noted. The entire ventricle was not filled with air, and the fluid level of the posterior horn was sharply defined.

but cooperated well on examination. Neurologic findings were essentially negative except the eye grounds, which showed the disk margins to be much blurred. In the right fundus, the disk margins could not be made out. New tissue was present, and there was perivascular streaking. The optic cup and lamina cribosa were filled with new tissue. No embedding of the vessels and

no measurable elevation of the disk were made out. Low grade choked disk of long standing, slightly more pronounced on the right side, was present.

A roentgenogram of the skull (Fig. 1) revealed a bony elevation near the coronal and sagittal sutures, which measured about 3 inches (7.6 cm.) in diameter and was elevated about ½ inch (1.27 cm.) above the flush of the

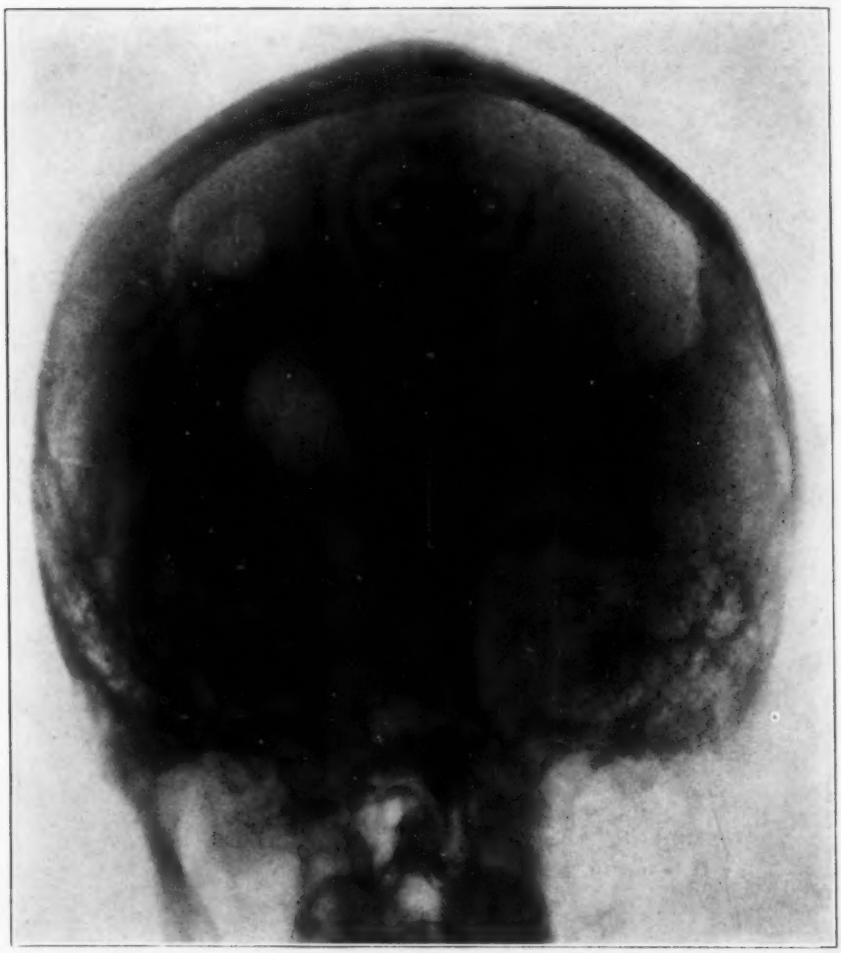

Fig. 5 (Case 1).—Anteroposterior view, showing the skull defect caused by removal of the bony growth in 1920; right lateral ventricle displaced downward and outward, and left lateral ventricle entirely closed by endothelioma.

skull. There was tremendous thickening of the skull about this elevation. In fact, it appeared to be 1½ inches (3.8 cm.), or more, in thickness. There was some definite new bone formation on the right side where the bone had been removed four years previously. The scalp was freely movable over this tumor mass, and no inflammatory reaction was noted.

Blood and spinal fluid Wassermann reactions were negative. Hemoglobin was 97 per cent.

Operations and Results.—In a two-stage operation, performed March 10 and March 17, 1920, I removed en masse what appeared to be a large osteoma (Figs. 2 and 3). It lay directly over the longitudinal sinus where considerable difficulty was encountered in freeing the projecting spicules of bone from the underlying tissues. The dura seemed to be frayed and torn; but no further exploration of the cortex was made at this time because the patient was tremendously shocked. Following this procedure, he made a very satisfactory convalescence, returned to work as an expert accountant and continued at work

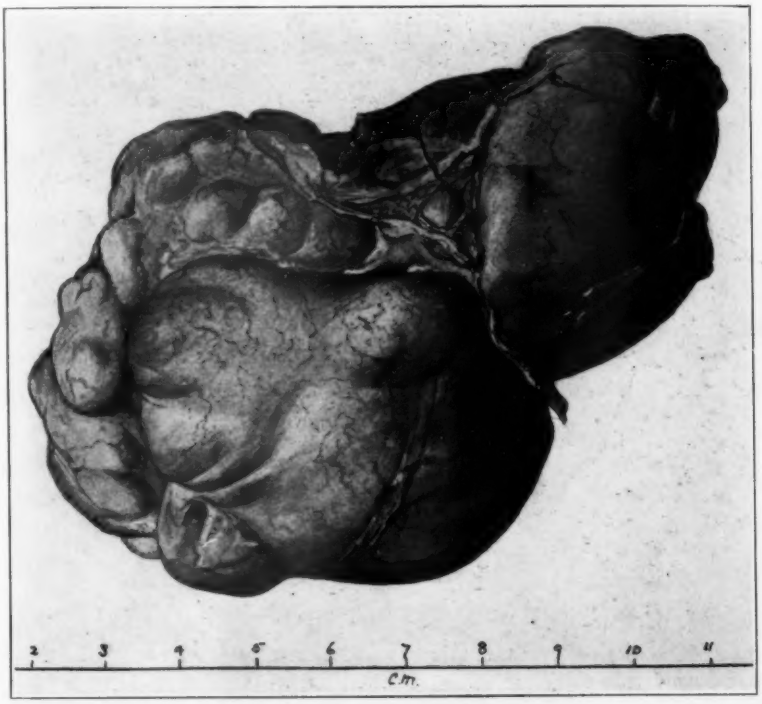

Fig. 6 (Case 1).—Endothelioma underlying bony growth (compare Figs. 2 and 3). The tumor growing within and from each side of the longitudinal sinus may be noted. The tumor mass on the right side was much smaller than on the left. It was removed en masse, with resection of the longitudinal sinus and falx cerebri; weight, 135 gm.

until his final operation in March, 1922. During this period, he was kept under bromids and phenobarbital (luminal) for much of the time. He was irritable and difficult to live with. In July, 1921, his irritability increased. Oct. 20, 1921, he had a very severe convulsion, the sixteenth, lapsing into a stupor which lasted for twenty-four hours. Four weeks later, he had another similar convulsion, the seventeenth. Feb. 23, 1922, the eighteenth and last convulsion occurred. This was general and very similar to the two just cited.

About this time, he became given to speculation, showed unsound business judgment, suicidal tendencies and again left home without apparent cause. Headache, while present, was not a prominent symptom. During this time, it was noted that there was never a depression over this large skull defect caused by the removal of the bony tumor in March, 1920.

Knowing that endotheliomas sometimes underlie bony overgrowths of the skull, I felt that the patient probably had such a tumor, which had not been disclosed at the former operation. Reexamination, March 7, 1922, revealed a recurrence of the bony tumor. Ossified areas could be palpated under the scalp in the region of the operative defect, some of which were free islands of movable bone, in no way connected with the surrounding skull but which undoubtedly had grown since the last operation.

Physical and neurologic examination at this time was again negative, except for the fact that the eye grounds showed a blurring of the disk margins

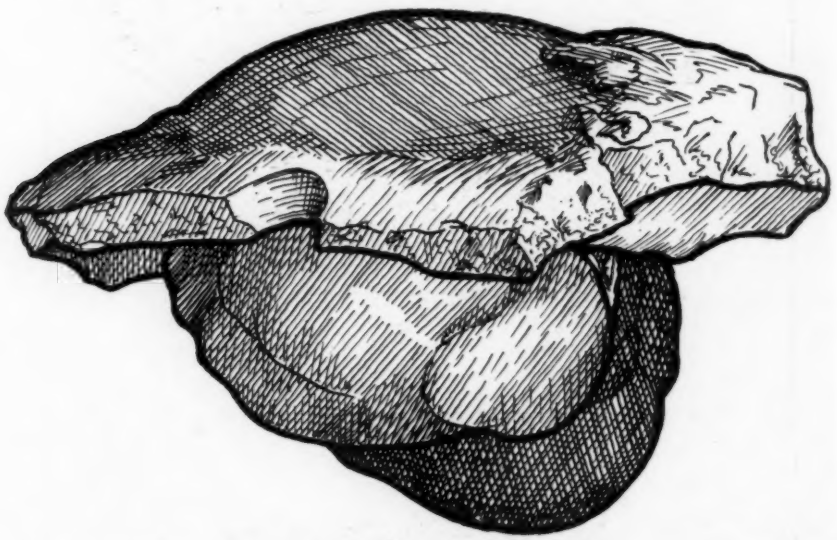

Fig. 7 (Case 1).—Diagrammatic reproduction of complete growth, showing bony and soft tumors in relative position; entire weight, 240 gm.

and congested vessels. This phenomenon was a recurrence, as the eye grounds had become practically normal following the removal of the bony growth two years previously. The main objective signs at this time were a recurrence of the tumor and extreme nervousness.

March 13, 1922, under local anesthesia, 35 c.c. of cerebrospinal fluid was removed from the right lateral ventricle and replaced by 35 c.c. of air. This procedure was carried out by the repeated removal of 5 c.c. of fluid, which was replaced by a similar amount of air until the total had been reached. The fluid was under moderate pressure and clear. The roentgen-ray examination of the ventricles (Figs. 4 and 5) demonstrated that the air was trapped entirely in the right ventricle, which was displaced outward and downward. On the lateral view, a distinct notch could be seen on the upper surface of the anterior horn of the right ventricle, which was interpreted as being caused by pressure

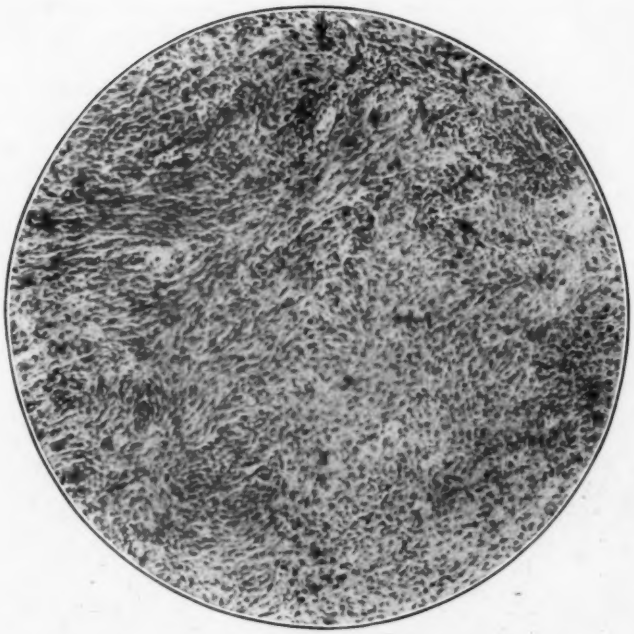

Fig. 8 (Case 1).—Section of endothelioma showing systems of flattened cells tending to whorl formation.

Fig. 9 (Case 1).—Appearance of patient three months after last operation.

from a lobular growth. The best explanation of the absence of air in the left ventricle and the displacement of the right outward seemed to be that there was a large growth projecting into each hemisphere, being larger on the left, so that the left ventricle was entirely closed, while the right was deformed and pushed outward.

March 20, 1922, the old operative field was reopened, and new bone was found growing throughout this region. There was also a recurrence of new bone from the margins of the skull defect; this was largely removed. The dura was then opened, and a tumor was found growing from both sides of

Fig. 10 (Case 2).—Lateral view of skull, showing osteoma in right frontal region.

the longitudinal sinus, involving it and apparently invading the brain proper. Several attempts to find a line of demarcation were unsuccessful.

The tumor on gross examination appeared to be malignant sarcoma, and sections were taken before closure. These sections were quite typical of endothelioma, and, March 27, 1922, the wound was again opened and an endothelioma weighing 135 gm. was removed en masse (Figs. 6 and 7). The longitudinal sinus was resected for a distance of about 10 cm. and was removed with the tumor. The tumor was encapsulated, and the mass growing from the left side of the longitudinal sinus was about twice as large as that growing from the

right side. In fact, after the removal of the tumor, the left side of the cavity reached to the floor of the anterior fossa and seemed to have blocked completely the left ventricle. The part of the tumor excavation on the right side extended down about half way to the floor of the anterior fossa. A large fascia lata graft was placed over the defect and the wound closed without

Fig. 11 (Case 2).—Anteroposterior view, showing osteoma above right orbit; growth attached to both the supra-orbital wall and the inner surface of the frontal bone.

drainage. The patient stood the operation well and left the hospital in two weeks.

Microscopic Examination (Fig. 8).—Dr. Roy Hammack of Los Angeles reported thus: "The tissue consists principally of whorls of flattened cells, sometimes spindle shaped with large oval nuclei. In some places, the whorls

are not seen and the cells are arranged in long bundles. Frequently, there is seen at the center of the whorl a small blood vessel. Diagnosis: endothelioma of meninges."

Comment.—Since the last operative procedure, the patient has been free from epileptic attacks, and the use of all sedatives has been discontinued. There is still undoubtedly some diseased bone about the edge of the skull defect, into which the scalp tends to dip. He has gained about 20 pounds in weight and is working again as an expert accountant (Fig. 9). The mental symptoms described above have improved considerably, and his wife states that he is more normal than she has known him for years.

CASE 2.—*History.*—E. H. E., man, aged 48, married, retired chaplain, United States Army, referred by Dr. Edward Dillon of Los Angeles, was admitted to St. Vincent's Hospital, April 17, 1922, complaining of severe frontal headache and epilepsy. When a child, he had scarlet fever, and all his life he had had double otorrhea. He was also said to have had malaria and spinal meningitis in 1904, and pulmonary tuberculosis and influenza in 1918. There was no history of head injury. His present illness began insidiously, about four years previously, and was ushered in by frontal headaches which had gradually increased in severity. Insomnia and extreme restlessness had been present

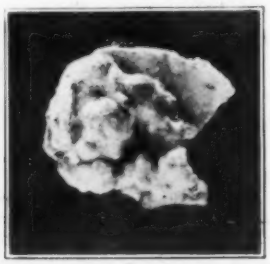

Fig. 12 (Case 2).—Appearance of tumor, showing nodular character of surface; no underlying endothelioma.

for the last three or four years. The nervousness increased markedly, and, about two years previously, the patient suffered from mental confusion for a period of two or three weeks, after which normal mental processes were regained. About eighteen months before admission, he became deranged mentally, and, following a severe convulsion, lapsed into a state of complete unconsciousness which lasted for ten days. In a month's time, he again regained full mental activity. About two months before admission to the hospital, the patient again suffered from mental agitation. He also complained of numbness and weakness in the left arm and weakness in the left leg. During the last six months, there had been times when he did not articulate well. His temperature had always been normal during these attacks and his pulse about 80.

Examination.—He was a tall man and much under weight, and he exhibited marked mental agitation. The head was rather large but quite symmetrical. Examination of the cranial nerves was negative, except for slight weakness of the left lower face. The eye grounds showed overfilling of the veins and some haziness of the disk margins, particularly on the right. No measurable swelling was made out. There was definite weakness of the grip in the left hand—left, 10; right, 80. The patient also complained of some

paresthesia in the left arm and hand; but no sensory changes were noted on objective examination. There was no hemianopia, and no astereognosis, right or left. The patient stood fairly well in the Romberg position. The gait was somewhat unsteady; but there was no definite ataxia. There was, however, moderate ataxia in performing the finger to nose and the finger to finger test, so that a question arose in the mind of one examiner as to whether the patient might not be suffering from a cerebellar lesion. The superficial reflexes were present and about normal. The deep reflexes were increased on the left side. The Babinski reflex was positive on the left, and negative on the right. There was no ankle clonus on the left or right.

Fig. 13 (Case 2).—Postoperative lateral view, showing defect resulting from tumor removal.

The roentgen-ray examination of the skull (Fig. 10) revealed a dense shadow measuring about 2 cm. in diameter. This shadow appeared to occupy an area in the right frontal region, about midway between the front of the orbit and the anterior clinoid process. In the anteroposterior view (Fig. 11), it appeared above the middle of the orbit. There seemed to be a pedicle attaching this growth to the floor of the anterior fossa or roof of the orbit.

The laboratory findings were as follows: temperature, 98.6 F.; pulse, 70; erythrocytes, 4,250,000; leukocytes, 6,996; differential count: mononuclears, 26 per cent.; polymorphonuclears, 72 per cent.; transitionals, 2 per cent.;

hemoglobin, 70 per cent. The blood Wassermann reaction was negative. The results of urinalysis were: reaction, acid; color, yellow; specific gravity, 1.012; albumin, faint trace; sugar, negative; casts, none. The blood pressure was 101 systolic, and 68 diastolic.

Operation.—April 27, 1922, a right osteoplastic flap was turned down in the frontal region. The flap was outlined with the base on the temporal side, and Frazier's technic for frontal approach to the pituitary fossa was employed. There were many large blood vessels in the scalp, and considerable bleeding occurred because it was impossible to use a tourniquet. On making the last trephine opening just above the orbit, the operator unexpectedly encountered the tumor itself. However, the flap was turned down as outlined, and the tumor was turned up with the flap. The tumor was then removed with a small margin of normal skull (Fig. 12). In doing this, it was necessary to enter the top of the right orbit and expose the orbital contents. Even then, it was not certain that all the bony overgrowth had been removed. When the flap was turned back, the dura, which was closely adherent to the tumor, was found to be shredded and torn. A large dural flap was then turned back, and the frontal lobe

Fig. 14 (Case 2).—Appearance of patient, ten days after operation; defect in right frontal region occasioned by tumor removal may be noted.

inspected. It was soft and somewhat discolored just under the site of the tumor; but nothing that appeared to be an endothelioma was found. The wound was then closed in layers without drainage. The patient made an uneventful convalescence. All sutures were removed, May 4, and the patient left the hospital, May 10, 1922, two weeks after the operation.

Comment.—In reading the roentgenograms, I was misled. There appeared to be a pedicle attaching the tumor to the floor of the anterior fossa. As a matter of fact, the tumor was directly attached to the lateral surface of the inner table of the skull, just back of the external angular process and to the roof of the orbit and was inadvertently encroached on in turning back the flap (Fig. 13).

July 13, 1922, the patient (Fig. 14) had had no further epileptic seizures and did not complain of headache. He had become clear mentally and was much less nervous than before the operation. He had gained about 40 pounds in weight, and the weakness of the left hand, arm and leg had practically disappeared.

ALTERATIONS IN THE CURRENTS AND ABSORPTION OF CEREBROSPINAL FLUID FOLLOWING SALT ADMINISTRATION *

FREDERIC E. B. FOLEY, M.D.

ST. PAUL

Recent investigation has shown that, in experimental animals, both the pressure of the cerebrospinal fluid and the bulk of the brain can be reduced, either by the administration of hypertonic solutions intravenously,[1] or by the ingestion of salt.[2] The present paper deals with the alterations in the absorption and circulation of cerebrospinal fluid accompanying these changes in fluid pressure and brain bulk.

This fall of fluid pressure might at first glance appear to be due to decrease of brain volume. In such case no essential alteration in the processes of fluid absorption or secretion would need to be inferred. However, the diminution of brain volume does not wholly account for the lowering of fluid tension. This became apparent during the progress of one of the investigations mentioned above.[2] Certain observations, to be detailed later, were made which indicated that the fall of fluid pressure was actually due to a disturbance in the fluid-absorbing and fluid-producing mechanisms. There was also evidence of marked alteration in the normal currents of fluid in the ventricular system and cerebrospinal spaces.

Conjointly with these laboratory experiments, a clinical study of the uses of salt in conditions of increased intracranial tension was being conducted on Dr. Cushing's service at the Peter Bent Brigham Hospital.[3] This study gave abundant proof that the decrease of fluid pressure and brain bulk, produced in laboratory animals by salt administration, could be similarly produced in the human subject. In individuals whose cerebral ventricles were obstructed and dilated, salt ingestion was much more effective in lowering cerebrospinal fluid

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* From the Laboratory for Surgical Research, Harvard Medical School, Boston.

1. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentration, Am. J. Physiol. **48**:512 (May) 1919; Experimental Alteration of Brain Bulk, ibid. **48**:531 (May) 1919.

2. Foley, F. E. B., and Putnam, T. J.: The Effect of Salt Ingestion on Cerebrospinal Fluid Pressure and Brain Volume, Am. J. Physiol. **53**:464 (Oct.) 1920.

3. Foley, F. E. B.: Clinical Uses of Salt Solution in Conditions of Increased Intracranial Tension, Surg., Gynec. & Obst. **33**:126-136 (Aug.) 1921.

pressure and diminishing brain bulk than was the case when these conditions were absent. This striking feature of the observations on patients was unexplained. It was suggested that absorption of the hydrops from within the ventricles would account for the response. However, absorption is thought not to occur in this situation.

It was believed that a systematic investigation of the changes in fluid absorption and circulation occurring in animals as the result of salt administration might be of considerable physiologic interest, and, at the same time, might offer a solution of the unexplained responses to salt administration seen in patients with obstructed and dilated ventricles.

SUMMARY OF THE NORMAL ANATOMY AND PHYSIOLOGY

It may be serviceable at this point to summarize briefly the accepted beliefs concerning the anatomy of the fluid spaces and the production, circulation and absorption of the fluid.

The ventricular system consists of the two lateral ventricles communicating with the third ventricle by means of the two foramina of Monro. The third ventricle in turn is joined to the fourth by the aqueduct of Sylvius. From here the ventricular system opens into the cisterna magna, a part of the subarachnoid space, by means of the foramen of Magendie, a median defect in the pial fold and epithelial roof of the fourth ventricle which extends from the posterior medullary velum in front to the medulla behind, and also by the foramina of Luschka, two openings at the extremities of the lateral pockets.

The choroid plexuses appear to lie free in the ventricles, though actually they are extraventricular structures, for they consist of masses of fine convoluted vessels lying outside the continuous layer of ependyma which constitutes the inner surface of the ventricular walls. These masses of vessels receive a complete investment of ependymal epithelium which thus becomes invaginated over them and excludes them from the ventricular cavities proper very much as the peritoneal covering of the intestines excludes them from the peritoneal cavity. Similarly, the sheets of ependymal epithelium which, after covering the choroidal vessels, extend back to the nervous tissue proper might be compared to the leaves of the mesentery. The ependymal leaves are termed the lamina chorioidea. In the third ventricle they are attached to the margins of the thalamus along a line known as the taenia thalami. From these attachments the invaginated choroid hangs down into the ventricle. The invagination is continued forward and laterally on both sides between the thalamus and fornix so that it projects into the lateral ventricles as the choroid plexus of these cavities. Here the upper leaf of the lamina chorioidea is attached to the margin of the fornix, while the lower leaf is attached to the dorsal surface of

the thalamus. The choroid plexus of the fourth ventricle is formed by a mass of vessels carried into the ventricle with an investment of epithelium from the thinned out roof extending below the cerebellum.

The extraventricular fluid spaces or subarachnoid space is made up of the irregular crevices formed by the irregularities of the brain surface and by the space intervening between the brain and skull. On the side of the brain this space is lined by a continuous mesothelial membrane, the pia, which closely invests the brain, dipping into the depths of all the sulci and other surface irregularities. On the side of the skull it is lined by another continuous mesothelial membrane, the arachnoid, which lies in contact with the dura and bridges the brain irregularities. This cranial subarachnoid space is continuous with the spinal subarachnoid space which in a similar way intervenes between the pia of the cord and the spinal arachnoid.

The main portion of the cerebrospinal fluid is a product of the choroid plexuses. That which is poured out in the lateral ventricles passes through the foramina of Monro to the third ventricle. Here the third ventricle choroid adds to the volume, and the current continues downward through the aqueduct and, with the addition from the fourth ventricle, is discharged into the subarachnoid space through the foramina of Magendie and Luschka. In the subarachnoid space there is a second source of supply of an entirely different sort, and one concerning which some doubt still exists. This comes from the perivascular spaces surrounding the vessels of the brain substance. These spaces exist as a defect between the walls of the cerebral arteries and veins and a surrounding envelop of mesothelial or glial cells. In the substance of the nervous tissue they join other spaces surrounding axons and larger nerve cells. On the surface they open into the subarachnoid space at the points of emergence of the vessels. Mott [4] first described a flow of fluid in these spaces as from the subarachnoid space to the brain substance and believed them to be channels of fluid absorption. Weed,[5] however, in a very comprehensive reinvestigation of this whole subject, concluded that under normal circumstances the flow is in the opposite direction, from brain substance to subarachnoid space (thus reverting to a conception favored previous to Mott's work), and that these spaces must be regarded as sources of cerebrospinal fluid. Without entering into a discussion of the evidence it may be said that it supports the latter conclusion.

From the subarachnoid space the fluid is absorbed into the dural sinuses along the arachnoid villi—small tufts of arachnoid cell masses

4. Mott, F. W.: The Oliver-Sharpey Lectures on the Cerebrospinal Fluid, Lancet **2**:1, 79, 1910.

5. Weed, L. H.: Studies on Cerebrospinal Fluid, J. M. Research **26**:93 (Sept.) 1914.

which project into these blood streams through clefts in the dura forming the sinuses. In addition there is absorption along the sheaths of the cranial and spinal nerves, a stream which finally enters true lymphatic channels. There is no evidence in favor of absorption directly into the small vessels which traverse and are supported in the subarachnoid space.

EXPERIMENTAL INVESTIGATION

1. *Method.*—Cats were used for all the experiments. The methods employed were various applications of the procedures used by Weed in his brilliant contributions in this field.[5] In a general way the experiments may be separated into two types: first, those dealing with the volume of fluid absorbed from the subarachnoid space and ventricles, or ventricles alone, after salt administration, together with determinations of the accompanying pressure change; and second, gross and microscopic identification of material precipitated from a foreign solution supplied to the subarachnoid space or ventricles following salt administration. The salt was administered as a 30 per cent. solution of sodium chlorid, either intravenously or into an exposed loop of the duodenum. The animals were anesthetized with urethane. The particular details of the method in the several experiments will be detailed in each case.

2. *The General Effect of Salt Administration on Cerebrospinal Fluid Pressure and Brain Volume.*—In a series of preliminary experiments which were a part of a former communication,[2] simple determinations were made of the cerebrospinal fluid pressure changes caused by salt. The pressures were measured in a manometer connected to a needle in the subarachnoid space introduced by occipito-atloidal puncture. The manometer was filled with physiologic sodium chlorid solution and set at 100 mm. of pressure. On giving the animal a small dose of 30 per cent. sodium chlorid, either intravenously or into the duodenum, the cerebrospinal fluid showed an extensive and well sustained fall of pressure. A large series of experiments demonstrated that cats of equal size, given the same dose of sodium chlorid under like experimental conditions, give curves of pressure change almost identical, both as regards the rate of change and the extent of fall. The experiments revealed that the responses are quantitative reactions governed by the amount of salt administered.

An additional effect of these solutions is a decrease in the size of the brain, as first described by Weed and McKibben.[6] The shrinkage of the brain enlarges the cerebrospinal fluid spaces. In view of this fact, the question naturally arose as to whether in experiments of this

6. Weed and McKibben: Footnote 1, second reference.

sort the fall of pressure recorded by the manometer might not be due simply to the dislocation of fluid from the manometer into the enlarging cerebrospinal fluid spaces and be indicative of no particular alteration in the fluid-producing and fluid-absorbing mechanisms.

3. *Proof of a Disturbance in the Ratio Between the Pressures Under Which Fluid Is Absorbed and Produced.*—The question was put to test by a series of experiments, as follows: Two cats of equal size were used for each experiment. To each animal a certain dose of 30 per cent. sodium chlorid was given. In one animal the cerebrospinal fluid pressure was recorded in a manometer of such bore that 100 mm. of pressure change required a displacement of 1.06 c.c. of fluid, while in the manometer used for the other animal the same pressure change required a displacement of 0.26 c.c. of fluid. That a disturbance in the ratio between fluid production pressure and fluid absorption pressure is induced by the administration of salt is proved by the fact that the

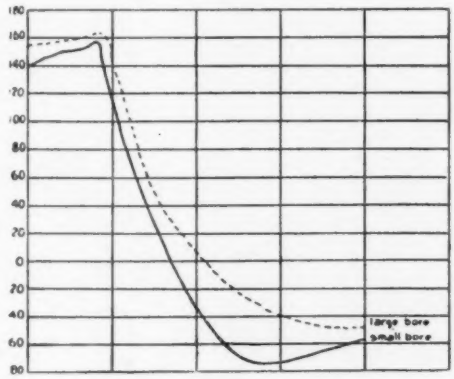

Fig. 1.—Curves of cerebrospinal fluid pressure of two cats, each of which weighed 3.8 kg. and was given 10 c.c. of 30 per cent. sodium chlorid solution intravenously. In one animal the pressure was recorded by a manometer of such bore that 100 mm. of pressure change required a displacement of 1.06 c.c. of fluid (broken line). In the other animal the pressure was recorded by a manometer of such bore that 100 mm. of pressure change required a displacement of 0.26 c.c. of fluid (continuous line). The approximate parallelism of the curves and the nearly equal falls of pressure may be noted.

curves of pressure change obtained by these different manometers parallel each other very closely and record pressure falls of about equal extent (Fig. 1). Were the changes in height of the fluid columns in the manometers simply a function of volume change in the cerebrospinal spaces, then one manometer being four times the size of the other should illustrate a pressure change one-fourth as extensive and at a very much lower rate. These changes have been demonstrated in numerous experiments of this sort and with manometers of various volume. Within the limits of the absorption mechanism to increase

its rate of taking up fluid, the curves have all shown this parallelism. They show that salt administration induces a change of cerebrospinal fluid pressure which is largely independent of the volume change occurring in the cerebrospinal spaces.

4. *Features of the Reaction to Be Studied: the Ferrocyanid Method.*—That an increased osmotic value of the blood is the agency through which these changes are brought about, there can be no doubt. Determination of these changes has been undertaken in a clinical study apart from the present work.[7] We have not concerned ourselves here with the fundamental osmotic disturbances occasioned by the salt administered, but we have sought rather to determine the alterations in the mechanical movements of the fluid and changes in its absorption.

Concerning these alterations in absorption numerous questions arose: Was there simply an increased rate of absorption along normal channels, or were new avenues of fluid escape opened? As a first step toward the solution of these problems, use was made of the ferrocyanid reaction as employed by Weed.[5] The reaction consists in the precipitation by hydrochloric acid of Prussian blue (ferric ferrocyanid) from a mixture of solutions of iron ammonium citrate and potassium ferrocyanid, with later identification of the precipitated Prussian blue in the situations to which the solution was carried or absorbed. The method of applying the reaction in these experiments was as follows: Equal amounts of 2 per cent. iron ammonium citrate and 2 per cent. potassium ferrocyanid solutions were made up and kept separate until used. A manometer with tubing and needle attached was then filled with the mixture and set at from 100 to 120 mm. of pressure—the pressure usually to be anticipated in the normal animal. By means of occipito-atloidal puncture the manometer was connected to the subarachnoid space. After a brief period allowed for the establishment of equilibrium and determination of the animal's normal pressure, salt was administered. According to the size of the animal from 10 to 20 c.c. of a 30 per cent. sodium chlorid solution was given either intravenously or into the duodenum. Incident to the giving of salt, the fluid showed the usual extensive fall of pressure. With falling pressure the ferrocyanid solution was displaced out of the manometer into the subarachnoid space. The amount of the solution so displaced was determined by the extent of pressure fall and the bore of the manometer used. At some period during the lowered pressure, usually when it had reached its full extent, precipitation of the Prussian blue and fixation of the brain were secured either by perfusion through the

7. The study referred to is being conducted on the medical wards of the Peter Bent Brigham Hospital (Wynn and Foley: Salt Administration as an Adjunct in the Intraspinal Treatment of Syphilis).

aortic arch with 10 per cent. liquor formaldehydi containing 1 per cent. of concentrated hydrochloric acid, or by immersing the head in 20 per cent. liquor formaldehydi containing 2 per cent. of the acid after first rongeuring away the greater part of the calvarium, leaving an intact dura. The perfusion, though it washed away the greater part of any precipitate in the vessels, assured immediate precipitation of the Prussian blue and fixation of the brain, and gave better material for histologic study. For the latter purpose, the tissue was washed, run through graded alcohols, and embedded in celloidin.

Paraffin sections are not suitable, for the dissolving of the paraffin in xylene releases the granules of Prussian blue which become free to float into situations in which they were not precipitated.

Fig. 2.—Drawing, showing the gross distribution of Prussian blue over the external surface of the brain; cat weight 3 kg.; ferrocyanid solution supplied to subarachnoid space from large bore manometer; 20 c.c. of 30 per cent. sodium chlorid injected into duodenum; 1.4 c.c. of ferrocyanid solution displaced in twenty-eight minutes, perfusion of aortic arch with 10 per cent. liquor formaldehydi containing 1 per cent. of concentrated hydrochloric acid. The abundant precipitate about the base and in the region of the tentorium may be noted. In comparison with controls the region of the sagittal sinus shows relatively little precipitate.

5. *Distribution of the Prussian Blue in Control Experiments.*—The procedure in control experiments in which the animal received no salt was the same except that, in order to secure a displacement of the solution into the subarachnoid space, a higher pressure in the manometer had to be maintained. The brains of these normal controls showed a distribution of the precipitated Prussian blue, corresponding very well to the findings of Weed [5] in his studies of the normal absorption. In such control animals the precipitate occurred throughout the subarach-

noid space but in particular abundance about the large cisterns and basal pockets. It was carried upward over the cerebellar and cerebral hemispheres in the sulci but occurred in smaller amount over the convolutions. A relatively heavy deposit about the tentorium and sagittal sinus seemed to indicate a prominent current along these situations. It had extended forward about the base and out along the sheaths of the cranial nerves. In the latter situation the precipitate could be grossly identified some distance beyond the points of exit of the nerves from the skull. It was also present in the arachnoid villi, the chief channels of fluid absorption. Below the foramen magnum the spinal subarachnoid space showed the deposit for only a short distance, from 3 to 5 cm. below the atlas, practically no deposit being present. On section of these control brains the ventricles were found free from any trace of the deposit, provided a relatively low injection pressure had been employed. With pressures of from 300 to 400 mm. of the solution, however, there was definite precipitate in the fourth ventricle and lower part of the aqueduct, while with pressures of from 100 to 200 mm., this did not occur. Likewise, on microscopic study, the brains injected under high pressure showed a little deposit along the perivascular spaces for short distances, while in the case of the lower pressures, this did not occur.[8]

6. *Distribution of the Prussian Blue in Animals Given Salt.*—The brains of animals given salt showed striking differences from the controls in the amount and distribution of the precipitate. In the first place, the usual salt administration experiment yielded a much more abundant deposit in certain of the normal channels than occurred in the controls. Brains taken at different intervals during injection showed that the solution had reached these sites more rapidly. Figure 2 is the reproduction of a drawing of the brain in such an experiment. The deposit about the basal pockets and along the nerve sheaths was very abundant and the penetration, even to gross examination, was obviously more extensive than in the controls. A much more abundant deposit in the choroidal fissure on the meshes of the tela chorioidea was also apparent. Grossly, the region of the sagittal sinus showed relatively less precipitate than the controls. An increased amount of precipitate in the arachnoid villi was not demonstrated, and, indeed, in the material studied, it was difficult to find the granules in these situations at all. Careful comparison by means of serial sections through a large number of villi, however, was not made, and the impression is based on the examination of the few villi encountered in single sec-

8. In his studies of the normal animal, Weed was able to secure injection of these spaces only by sudden extensive bleeding from the neck vessels unless very high (55 mm. Hg) pressures were employed.

tions. In addition to these quantitative differences, the solution had passed downward in the spinal subarachnoid space for practically its whole length and was found along the sheaths of the lumbar nerves. Microscopic examination revealed beautiful injections of the perivascular spaces deep along their course in the brain substance. This observation is in accord with similar observations by Weed and McKibben.[6] The injection of the perivascular spaces occurred even when the solution was supplied to the subarachnoid space under zero pressure, as was done in a few experiments by opening widely the suboccipital space and pouring the solution into the cistern (Fig. 3). The fact that this injection of the perivascular spaces occurs even under zero pressure and with an open skull is very good evidence that the solution does not reach these sites because of artificially altered pressure relationships,[9] but is carried along the perivascular spaces by a process of true absorption. The granules can occasionally be identified in the walls and lumina of the vessels surrounded by these injected perivascular spaces. In many cases the deposit could also be identified about axons and nerve cells. This was particularly true in the tissue immediately surrounding the lower and forward parts of the third ventricle. Most striking of all, however, was the fact that on section of these brains there was an abundant deposit throughout the ventricular system. The solution had been carried to the extremities of the lateral ventricles, both in the frontal and occipital lobes.

7. Consideration of Ventricular Volume Change as a Possible Cause of Retrograde Passage of Fluid to Ventricles.—The fact that the solution had been carried into the farthest reaches of the ventricular system under the influence of salt administration, while controls showed that this did not occur even when high injection pressures were used, made it seem possible that an intraventricular absorption of fluid was one of the direct effects of the salt. The experiments described, however, did not give conclusive evidence of this. The objection raised was that the shrinkage in the brain might have been accompanied by an enlargement of the ventricular cavities with aspiration of the solution from the subarachnoid space along the aqueduct, entirely in consequence of the altered volume relationships and in no way due to true absorption within the ventricles. By the method employed it was impossible to say what part of the fluid displaced from the manometer had passed to the ventricles and what part had been absorbed from the subarachnoid space.

In the experiments of Weed and McKibben,[6] striking alterations in the bulk of the brain had been observed following the intravenous

9. As might be argued when a manometer at artificially high pressure is connected to the subarachnoid space.

administration of hypertonic solutions. These findings were confirmed in a study[2] made later in which the salt was given by the gastrointestinal route, as well as intravenously. The former writers do not mention any change in the size of the ventricles, while in the latter study such changes were looked for and certainly were not striking. The chief alterations in the gross appearance of animal brains due to salt administration are in their external appearance. The convolutions become smaller and shrunken, while the sulci become wider and deeper. The whole mass contracts. After careful comparison of the ventricles of these shrunken brains with those from normal animals of equal size, we have been led to the conclusion that the ventricular volume remains almost constant.

8. *Direct Study of Ventricular Volume Changes and Intraventricular Absorption by Means of the Aqueduct Catheter Method.*—These observations made it seem unlikely that enlargement of the ventricles was the cause of fluid passing up the aqueduct. An attempt was made, however, to determine definitely the volume of fluid displaced into the ventricles and to separate any absorption occurring here from that occurring in the subarachnoid space. To this end a manometer was connected to a small rubber catheter introduced along the aqueduct and of such size as effectively to seal itself off from the subarachnoid space by its contact with the walls of the aqueduct.[10] The procedure is technically difficult and only a certain proportion of the experiments attempted were successful. The animal was fixed in the prone position with the neck flexed far forward so as to make wide the space between the occiput and atlas. After dividing the postcervical muscles and freeing them from the occiput, the occipito-atloid ligament was divided by careful dissection and the arachnoid membrane opened with fine scissors. It was occasionally necessary to bite off a part of the occiput with the rongeurs in order sufficiently to expose the region of the foramen of Magendie. An inch or so of a No. 5 F flexible rubber catheter was used. A paraffin bead was molded onto the end of this small rubber tube in order to make it smooth and avoid injury to the walls of the aqueduct. The tube thus prepared was connected to a manometer of small bore filled to zero pressure with warm physiologic sodium chlorid solution. The catheter was then carefully inserted

10. This method of ventricular catheterization was first employed by Weed and Cushing (Am. J. Physiology **36**:77, 1915) in a study of the secretory responses of the choroid plexus to posterior lobe hypophysis extracts. Their employment of the method was for the purpose of eliminating from the determinations of fluid formation rate the effects of volumetric changes of the subarachnoid space caused by the blood pressure changes incident to the injected gland substances and also for the purpose of diverting the fluid from its natural channels of absorption.

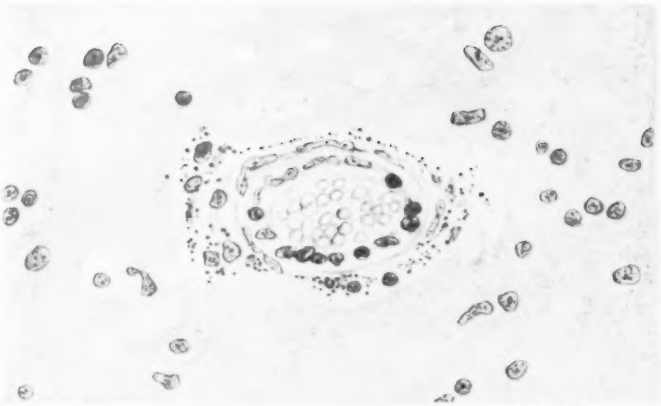

Fig. 3.—Drawing under high power to show the deposit of Prussian blue precipitated in a perivascular space to which the ferrocyanid solution had extended from the subarachnoid space. The ferrocyanid solution was supplied to the subarachnoid space under zero pressure by pouring it into the opened space between occiput and atlas. Fixation by immersion of brain in 10 per cent. liquor formaldehydi containing 1 per cent. of concentrated hydrochloric acid. The granules here are not deposited in the walls or lumina of the vessel as is often the case.

under the tip of the vermis and gently advanced a distance of from 18 to 22 mm. Tests disclosed that in the average sized animal this distance would put the beaded tip immediately under the quadrigeminal bodies, the narrowest and most substantial section of the canal. Figure 4 shows the catheter in situ and its relation to the surrounding structures. In the successful attempts, and in case the animal had not been exhausted from the long procedure, the column of fluid would show a typical pulsation when the manometer connection was opened. The pressure would gradually rise to a certain constant level and remain at this point. This pressure was usually considerably below the normal pressure recorded in the subarachnoid space of cats. This, I believe, may be attributed to the exhausting effects of the long operative pro-

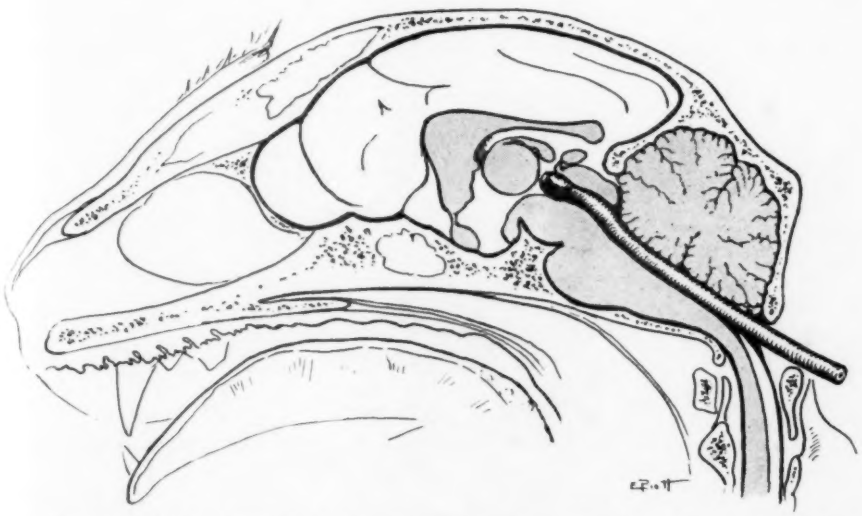

Fig. 4.—Sketch of midsagittal section through cat head to show the position and relations of the aqueduct catheter.

cedure rather than to any physiologic difference between intraventricular and subarachnoid pressures. The majority of animals showed intraventricular pressures of between 70 and 130 mm. of saline.

By this type of experiment, determinations were made of normal intraventricular pressures, and also pressure changes incident to the administration of hypotonic (water) and hypertonic (30 per cent. sodium chlorid) solutions. By measuring the amount of physiologic sodium chlorid solution which was displaced out of the manometer, the volume changes of the ventricle plus intraventricular absorption accompanying the salt administration were also determined. Finally, the microscopic distribution of Prussian blue precipitated from a ferrocyanid mixture supplied directly to the ventricles was studied. Only

experiments are here considered in which no possible leakage occurred between the catheter and the walls of the aqueduct. The perfection of this connection was tested at the end of each experiment by careful search of the cerebellar cistern for granules of Prussian blue. In some brains, not used for microscopic study, the perfection of the connection was tested by injecting the ferrocyanid solution into the catheter under a pressure far greater than the normal. If the precipitate of Prussian blue could be found anywhere in the subarachnoid space it indicated leakage, and the experiment was discarded. Figure 5 is reproduced from a drawing of a cross section through the aqueduct and catheter, showing the latter in situ. It shows the intimate contact of the catheter with the aqueduct.

In brief, it may be said that under the experimental conditions described, intraventricular pressure has shown changes and responses to test solutions qualitatively similar to those recorded in the subarach-

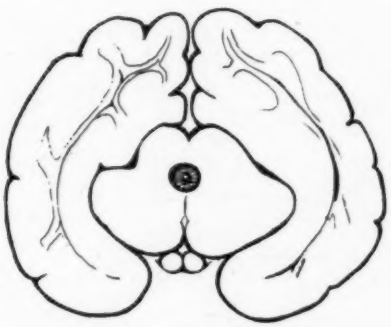

Fig. 5.—Transverse section through the aqueduct and catheter, showing intimate contact between catheter and walls of the aqueduct.

noid space. The changes, however, are produced more rapidly and are not quite so well sustained. Curve A in Figure 6 shows the effect on intraventricular pressure of an intravenous injection of 30 c.c. of distilled water. A rise of 22 mm. in pressure occurred—very much less than the rise of pressure usually produced in the subarachnoid space of an animal of this size following such a dose of water. Curve B shows the fall of pressure caused by an intravenous injection of 7 c.c. of 30 per cent. sodium chlorid solution. Here the effect is more nearly comparable to similar changes produced in the subarachnoid space—a fall of 50 mm. The rate of fall, however, is considerably more rapid. In most cases the fall of pressure is preceded by a small preliminary rise.

Determination of the amount of fluid displaced into the ventricles following salt administration demonstrated quite conclusively that intraventricular absorption had occurred, for the volume of fluid so dis-

placed was far in excess of any possible ventricular volume changes. Details from a typical experiment may be cited: The manometer was of such bore that 100 mm. of pressure change required a displacement of 0.2 c.c. of fluid; it was filled with physiologic sodium chlorid solution. The animal (cat weight 1.9 kg.) was given 8 c.c. of 30 per cent. sodium chlorid solution intravenously, a relatively large dose. The intraventricular pressure fell from 155 mm. to minus 13 mm. This represented a fluid displacement of 0.34 c.c. In relation to the volume of the ventricles of such a small animal this is a large amount of fluid. Though possible, it seems unlikely that a change of such volume occurred. In other experiments, however, either a manometer of larger bore was used, or after the pressure had fallen in the small manometer enough fluid was repeatedly added to raise the pressure from 20 to 30 mm. above the existing level. By these means amounts of fluid in

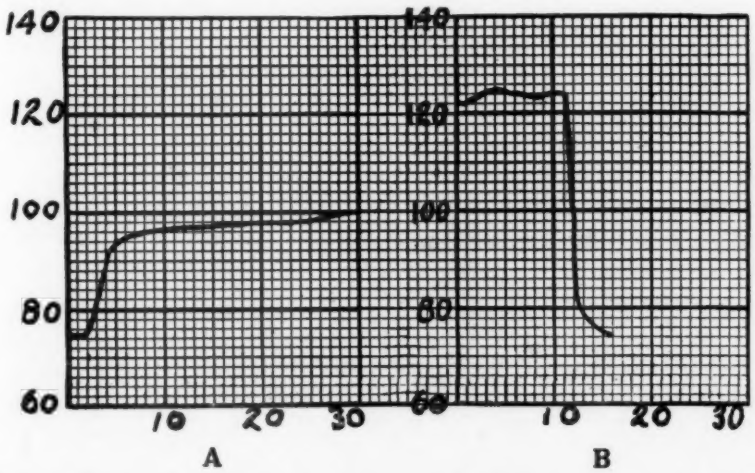

Fig. 6.—Curves of intraventricular pressure changes: *A*, the rise of intraventricular pressure following the administration of 30 c.c. of distilled water intravenously. Immediately after the injection is begun the pressure begins to rise rapidly. The elevated pressure is well sustained. Twenty-two minutes after the injection the pressure remains 22 mm. above its level before giving the water; *B*, the fall of intraventricular pressure following the administration of 7 c.c. of 30 per cent. sodium chlorid solution intravenously. Immediately after the injection is begun a precipitous fall of pressure occurs. Five minutes after the injection, the pressure is 50 mm. below its previous level.

excess of 1.5 c.c. have been displaced into the ventricles and under technically perfect conditions, an intact connection of the catheter in the aqueduct having been demonstrated in all cases on which the conclusion is based. The experiments show that under the influence of salt the ventricles will take up fluid greatly in excess of possible change in ventricular volume. They made it quite clear that the passage of the ferrocyanid from the subarachnoid space to the ventricles, as in the

experiments previously described, was in consequence of true intraventricular absorption and was not due to an increase in the volume of these cavities.

9. *Retrograde Absorption Through the Choroid Plexus and Ependyma.*—In a previous section the gross differences were pointed out between the distribution of precipitated Prussian blue in animals receiving salt and in normal controls. Mention was also made of the microscopic finding of the deposit in the perivascular spaces, indicating a reversal of the fluid current along these channels and their behavior as absorptive mechanisms under the influence of salt. In those experiments the ferrocyanid mixture was supplied to the subarachnoid space under various pressure relationships. By employment of the aqueduct catheter method, the solution was also supplied directly to the ventricles. Under these circumstances an abundant deposit of the Prussian blue was, of course, found in the ventricles. A description of the microscopic distribution of this precipitate within the ventricles as found in both types of experiment was deferred to this point in order, first, to present the experiments demonstrating that ventricular volume changes could not entirely account for its presence here, and secondly, to indicate that intraventricular absorption had actually taken place.

Greatest reliance has been placed in the sections taken from brains fixed by immediate perfusion with the acid containing liquor formaldehydi rather than in those fixed by immersion. In addition to these two methods of fixation, some of the brains in which the solution had been supplied to the subarachnoid space were prepared by first thoroughly washing away the ferrocyanid solution on the surfaces and pouring the fixative directly into the ventricles which were then laid open by tearing apart the corpus callosum. By this method not only were prompt precipitation and fixation assured, but the possible momentary osmotic effects of the perfusate in the vessels also was reversed. In all essential details the three methods have given the same microscopic distribution of the Prussian blue.

The deposit of Prussian blue is found lying free in the ventricular cavities, adherent to the ependymal epithelium and heavily deposited in the meshes of the choroid plexuses. It penetrates the farthest reaches of the ventricular system and in the lateral ventricles is carried far up into the angle between the fornix and thalamus, here lying between the ependyma proper and the laminae chorioideae. It lies in very intimate contact with the ependymal cells, and in many places is found deposited between them. This intimate relationship to the ependyma is most marked in the forward and lower parts of the third ventricle. Here the solution has everywhere extended beyond the ependymal lining, and the deposit is found in tissue spaces within the brain substance and in the perivascular spaces and lumina of the minute

Fig. 7.—Drawing under low power to show the precipitated Prussian blue in relation to lateral ventricle choroid plexus; same brain as in Figure 3. Section was taken transversely through the right lateral ventricle and shows a portion of the contained choroid plexus. Much of the precipitate no doubt was washed away. The abundant deposit over the ependyma and its relation to the surface of the epithelial cells of the plexus may be noted. All of the vessels show deposits about the endothelium, and in places the precipitate occurs within the lumen of the vessel.

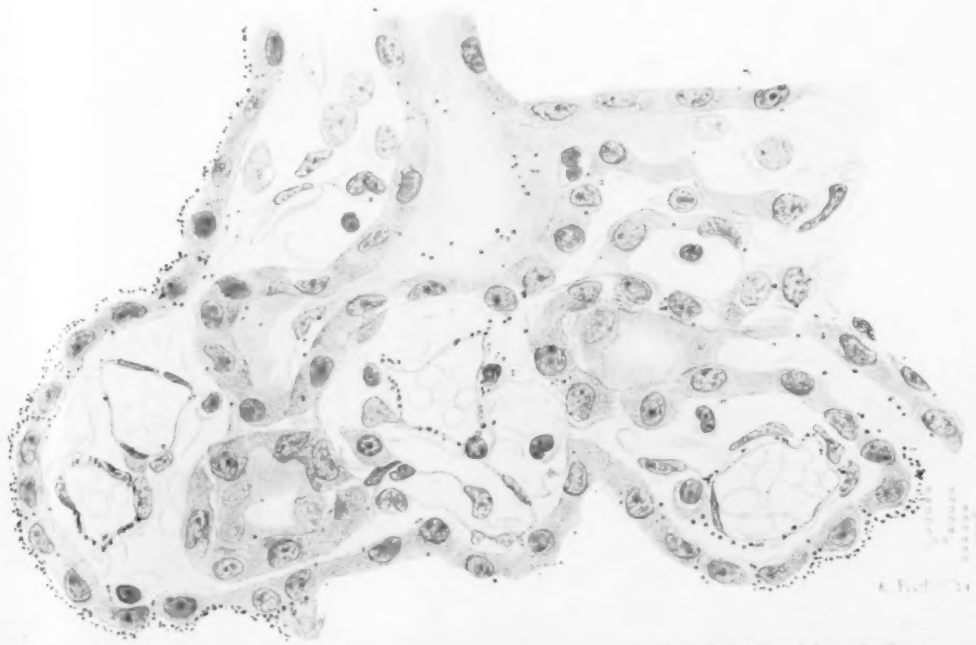

Fig. 8.—Drawing under oil immersion to show the detailed relationship of the precipitated Prussian blue to the structures of the choroid plexus. The abundant deposit over the surfaces of the cells and its apparent passage between the cells toward the capillaries may be noted. The vessel at the right shows the deposit lying between the epithelium and the wall of the capillary. In some situations the deposit appears to lie in the capillary wall, and in places it may be seen adherent to the inner surface of the endothelium. Any precipitate which might have lain in the lumina has been washed away by the perfusate. The animal was given 13 c.c. of 30 per cent. sodium chlorid solution intravenously. The ferrocyanid solution was supplied to the subarachnoid space from a manometer of large bore; 1.61 c.c. of the solution was displaced into the subarachnoid space under diminishing pressure, the injection having been begun when the cerebrospinal fluid pressure was at 142 mm. Brain fixed by perfusion of the aortic arch with 10 per cent. liquor formaldehydi containing 1 per cent. concentrated hydrochloric acid.

vessels in this region. That at least a portion of the solution reaches these sites by passage from the ventricle outward there can be no doubt, for it occurs when the solution is supplied to the ventricle alone, as well as when supplied to the subarachnoid space.

Most interesting is the distribution of precipitate in relation to the choroid plexus. It is intimately deposited about the epithelial cells of the tufts. From these situations it can be followed into the vessels of the tufts and is also found in the spaces intervening between the epithelium and the vessels. The intraventricular distribution of the Prussian blue as seen under low magnification is shown in Figure 7. The section was taken transversely through the right lateral ventricle and shows a portion of the contained choroid. Figure 8 shows the detailed relations of the granules to the epithelium of the choroid and the capillary vessels of the tufts as seen under oil immersion.

Certain minor differences may now be pointed out between subarachnoid and direct ventricular injections of the ferrocyanid mixture. In the case of subarachnoid injections abundant precipitate is found in the choroidal fissure clinging to the meshes of the tela chorioidea. In some cases the distribution of Prussian blue makes it appear that the solution has traveled along in this extraventricular situation out as far as some of the coarser tufts of the choroid, and has come along this extraventricular channel to lie in very close relationship to the smaller vessels of the plexus. Such granules would not represent an intraventricular absorption. That this channel is not the chief pathway of absorption into the vessels of the choroid is shown by the fact that absorption into these vessels takes place when the solution is supplied directly to the ventricle, with exclusion of these extraventricular channels about the tela chorioidea. Finally, in certain experiments, the aqueduct was obstructed by the catheter and the solution supplied, not to the ventricle, but to the subarachnoid space under zero pressure, by pouring it into the opened space between occiput and atlas. Under these circumstances the granules did not pass along between the laminae chorioideae to the smaller tufts but were present only about the larger vessels in the choroid fissure.

Finally, mention may be made of an alteration in absorption under the influence of salt consisting in the direct passage of fluid into the vessels traversing the subarachnoid space. In control animals there is occasional evidence of the same occurrence only when abnormally high injection pressures are employed. Controls injected under pressures of from 100 to 200 mm. of the solution showed no deposit in the walls or lumina of these vessels and the process cannot be said to be a part of normal absorption. All of the animals given salt, however, even if the ferrocyanid solution was offered to the subarachnoid space under zero pressure, showed granules deposited within these vessels.

SUMMARY AND COMMENT

The experiments described demonstrate that the curves of pressure change in the subarachnoid space resulting from salt administration, though possibly influenced by decrease of brain bulk and enlargement of the cerebrospinal spaces, are, nevertheless, fundamentally expressions of a profound disturbance in the mechanism of cerebrospinal fluid absorption.

The altered absorption causes changes in the grosser currents of the fluid. There is an increase of the current forward about the base and downward into the spinal subarachnoid, while the current upward along the sagittal sinus is relatively diminished. The current of fluid in the aqueduct is completely reversed, a retrograde flow from subarachnoid space to the lateral ventricles being established. Determinations of the volume of fluid which so passes to the ventricles demonstrate that the retrograde flow is in consequence of intraventricular absorption and cannot be attributed to increase of volume on the part of the ventricles.

The disturbance in absorption itself consists in an altered rate of fluid passage along certain normal channels and the opening up of other channels through which normal absorption does not occur. There is an increased rate of absorption along the sheaths of the cranial and spinal nerves, with possibly decrease or cessation along other normal channels—the arachnoid villi. Conclusive evidence, however, is not offered in favor of the latter. Under the experimental conditions described a reversal of flow in the perivascular spaces has been shown to occur and confirms the similar observation by Weed and McKibben.[6] This reversal of flow is due to absorption into the capillaries of the brain substance. Absorption directly into the vessels traversing the subarachnoid space is also established.

Finally, it is shown that the intraventricular absorption induced by salt takes place through the choroid plexus into capillary loops of the choroid vessels and through the ventricular ependyma into tissue spaces, particularly in the region of the third ventricle. The fluid absorbed through the latter channel finally reaches the perivascular spaces and vessels of this region.

The details of these alterations in the absorption mechanism which result from salt administration offer an adequate explanation of the fact that patients with an obstructive hydrocephalus show marked symptomatic improvement following salt administration. The reaction in these cases is due to intraventricular absorption of the dammed-up fluid. The salt induces absorption of fluid within the ventricles where normally no absorption takes place.

The results of this study invite much speculation as to certain features of the reaction to salt administration which have not been touched on. There is certainly an increased volume of the total fluid containing spaces within the cranium, owing to the great decrease of brain bulk. This factor, coupled with the markedly increased absorption of fluid along certain normal channels, and, in addition, the establishment of drainage along new pathways, leaves unexplained the factor which compensates for this outpouring from the "closed box." A compensating factor either in the form of increased volume of the intracranial blood vessels, or a supply of cerebrospinal fluid from some source, seems to be a physical necessity. It is difficult to believe that such an extensive vascular readjustment takes place. A retrograde flow of fluid in the aqueduct and the establishment of intraventricular absorption make it seem unlikely that the compensating factor is in fluid produced by the choroid plexus. The same argument applies to the perivascular spaces as a possible source of supply.

A suggestion as to where the compensating source of fluid may be is found in the fact that the increased absorption along normal channels, and that along the new channels opened by salt administration, occurs at points where the process is probably one of osmosis. The absorption via the nerve sheaths is doubtless ultimately due to a process of osmosis through the capillary walls separating the blood stream from the lymphatic spaces into which the fluid is passed by the nerve sheaths. That which occurs backward into the perivascular spaces is most likely in consequence of an osmotic process occurring through the cerebral capillaries separating the perivascular spaces from the blood stream. The same sort of process must account for the passage of fluid into the vessels of the choroid and those traversing the subarachnoid space. At the arachnoid villi, on the other hand, normal absorption is thought to be a process of filtration and to take place in consequence of a higher pressure existing in the subarachnoid space than in the sinuses.[5] It seems possible that the great fall of pressure in the subarachnoid space incident to the administration of salt reverses the flow through the arachnoid villi which, under these circumstances, would become sources of cerebrospinal fluid supply and could act as the compensating mechanism. Our failure to demonstrate increased absorption about these structures, as a result of salt administration, is suggestive.

CONCLUSIONS

1. Salt administration establishes a new ratio between cerebrospinal fluid production and absorption pressures, resulting in decreased tension of the fluid in the subarachnoid space and ventricles of the brain.

2. Salt administration induces these changes in the mechanism of fluid absorption: (*a*) intraventricular absorption through the choroid plexus and ependyma; (*b*) absorption by the capillaries of the brain substance with reversal of fluid flow in the perivascular spaces; (*c*) an increased rate of absorption along the sheaths of the cranial and spinal nerves, and (*d*) direct absorption into the vessels traversing the subarachnoid space.

3. The administration of salt causes alterations in the gross currents of the fluid which are incident to the changes in the mechanism of cerebrospinal fluid absorption described above. Chief among these alterations in the currents of the fluid is reversal of flow in the aqueduct and ventricular system.

THE RELATION BETWEEN OBLIQUE INGUINAL HERNIA AND WORKMEN'S COMPENSATION LAWS

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I. INTRODUCTION

Berger, in the opening sentence of his well known monograph, goes far to explain the entire foundation of the voluminous discussion as to hernia and accidents when he says, "There is not an individual who, having a hernia, at the moment when he noticed its existence, did not at once attribute it to an accidental cause, most often to an effort."

So we have a fixed idea inherent in the human race to combat, as well as the opinion of referees, boards and courts. Many surgeons believe that practically no hernias are of traumatic origin and that they should not be compensated; many labor leaders and social workers believe that all hernias are traumatic and that all should be compensated. The logic of the matter is just the same as it always is in the case of extremes, namely, that the truth lies somewhere between the two.

The present paper is the result of an effort to approach close enough to this intermediate point to form a fair and practical working basis. This effort is the outcome of a feeling that I have had for several years that the present legal and lay attitude is unsound, unscientific, at variance with firmly established medical facts, and that the attitude of courts and compensation boards is chaotic.

Several authors have attributed part of this confusion to the use of the word rupture as synonymous with hernia. A rupture is a tear, and what can cause a tear but an accident?—So there you are.

It has been shown that the English courts of the last century are responsible for a large part of the present difficulty. These courts floundered among directly contradictory medical witnesses; they did not have the benefit of sound scientific teaching which has been possible since hernia operations have become more common, and perhaps naturally they accepted "post hoc, ergo propter hoc" as the easiest argument. Medical men, indeed, had no very good ground for combating this attitude at that time. Our own courts and compensation boards have largely inherited the impressions of the English courts of a century ago and have not changed with the change of medical opinion.

The fault, however, is perhaps not so much with our legal confrères as with the medical profession. We have not impressed on courts and

boards the new knowledge developed by vast numbers of hernia operations performed since the days of Lister.

II. THE SACCULAR THEORY OF HERNIA

The connection between oblique inguinal hernia and the unobliterated processus vaginalis is the foundation of the present day medical conception as to the cause of hernia. Two French anatomists, Cloquet and Pellatin, in the eighteenth century called attention to the frequency with which this process persists. English writers, notably Kingdon and Macready, in the middle and latter part of the nineteenth century further called attention to this process and its connection with certain types of hernia.

It was not until 1899 that the full significance of the persistent processus vaginalis was definitely established by Russell, of Melbourne, Australia. It is interesting to trace briefly the development of Russell's work. At the Inter-Colonial Congress at Brisbane in September, 1899, Russell [1] read a paper entitled "The Etiology and Treatment of Inguinal Hernia in the Young." He contended that all inguinal hernias in the young are protrusions into a preformed unobliterated congenital sac—that the "acquired" hernia in the young was unknown. He cited in proof sixty hernia operations on children and infants in which the only procedure was obliteration of the sac. Russell's definite conclusions at this time are confined to children. However, even now he ventures the opinion that the same principle applies to adults, at least up to old age.

A year later, Russell [2] reiterated his views. He then had eighty cases of simple obliteration of the sac in children, with no failures, and he was more convinced of the case in adults. He concludes:

"1. Inguinal hernia in young subjects is caused by the presence of a congenital sac, and there is no other cause.

"2. Acquired hernia in the young has no existence in fact.

"3. All cases of oblique inguinal hernia occurring at any time of life occur in subjects who are the possessors of a congenital sac.

"4. Subjects who have never possessed a sac, or in whom the sac has been efficiently removed, can never become the subjects of oblique hernia.

"I am able to find no evidence of any kind in favor of the belief that oblique inguinal hernia ever occurs at any age, independently of the presence of a congenital sac."

In 1902, Russell's [3] list of operations in children was 115, only two of whom later showed a "slight weakness." "There is no difference etiologically between the inguinal hernia of children and that of older

1. Russell, R. H.: Lancet **2**:353 (Nov. 18) 1899.
2. Russell, R. H.: Lancet **2**:1128 (Oct. 20) 1900.
3. Russell, R. H.: Lancet **1**:1519 (May 31) 1902.

people." He[4] then changed his former opinions and posited a congenital sac also for femoral, obturator and ischiatic hernias.

Again, in 1905, Russell[5] expressed more firmly his previous views. Speaking then of adults, he says, "I have never met with a case on the operating table that I have seen any reason to regard as being a case of genuine acquired hernia. All my experience in surgery of adult hernia has been such as to force upon me the conclusion that there is substantially no difference between the hernia of adult life and that of childhood."

At that time, he believed that, even in adults, simple removal of the sac is nearly always sufficient.

So far as I know, Russell's[6] last paper appeared in 1906. In this he says, "A normal inguinal canal is fortified against the occurrence of a hernia to a perfection and a degree of strength in extravagant excess of any demand that can be made upon it by the feeble intra-abdominal pressure."

Later, he[7] said:

"1. Where there is no developmental sac such as is provided in the case of the inguinal canal by incomplete obliteration of the funicular process, there can be no hernia.

"2. The normally formed inguinal canal is endowed with a strength and retentive efficiency for resisting hernia, enormously in excess of any demand that can be made upon it by the mere intra-abdominal pressure unaided by the presence of a sac."

Russell soon received an active and militant supporter in Murray of Liverpool. Murray[8] published six articles from 1906 to 1907 and a book in 1910. He quotes dissections of 100 unselected adults without history of hernia. Twenty-one had a potential hernia sac, i. e., an unobliterated processus vaginalis; seven had more than one sac, and one had four. Later, he reports 200 dissections. Forty-seven bodies had sacs, often multiple, so that there were sixty-eight sacs in all.

Murray says, "I firmly believe in the truth of Russell's contention as to the congenital origin of the so-called acquired hernia."

III. THE LITERATURE

The saccular theory being now well launched, the opinions of medical writers on this and allied points connected with the etiology

4. Russell, R. H.: Lancet **1**:707 (March 12) 1904.

5. Russell, R. H.: Intercolon. M. J. Australasia **10**:408-424, 1905.

6. Russell, R. H.: Lancet **2**:1197 (Nov. 3) 1906.

7. Russell, R. H.: Lancet **1**:683-685, 1907.

8. Murray, R. W.: Lancet **2**:1246, 1904; Liverpool M.-Chir. J. **26**:207-210, 1906; Lancet **1**:363-365, 1906; Brit. M. J. **2**:1385-1389, 1907; Lancet **1**:1113; ibid. **2**:445 (Aug. 17) 1907; Hernia: Its Cause and Treatment, Ed. 2, London, 1910.

of hernia are of interest. In this review it has been obviously impossible to read all the articles on hernia, but I have carefully read every available article listed in the *Index Medicus* (about 200 in all), the title of which in any way suggested a discussion of etiology, trauma, compensation, etc. Only those articles which were found to have a special bearing are noted below.

BRITISH AND COLONIAL LITERATURE (EXCLUDING RUSSELL AND MURRAY)

Kingdon[9] (London, 1864) draws attention to the importance of the unobliterated processus vaginalis and holds it connected with certain phases of the development of hernia. He describes the popular belief in regard to strains, etc., and describes patients who think they strained themselves and noticed a hernia a few days later, and considered the strain to be the cause. The beliefs and statements of the patients in 1864 were evidently exactly the same as they are now. He says, "There is no evidence whatever to show that muscular exertion in health and by itself is ever a cause of hernia....All cases spring fundamentally from the same cause, namely, fault in the peritoneum. Hence it is concluded that hernia is a disease and not an accident, a pathological condition, not a mechanical lesion." (This in 1864.)

Macready[10] (London, 1893): "There are a great number of ruptures of which the contents are in an unobliterated part of the processus vaginalis, and it is impossible to distinguish these clinically, except in rare instances, from ordinary ruptures and not always even by dissection. We are seldom able to use correctly the term acquired.

"The name rupture also is open to objection because it implies an opinion as to the mode of formation of the disease which has long since proved to be erroneous.

"There is no positive assurance that intra-abdominal pressure causes hernia at a given moment of time in a person whose abdominal wall is normal."

Stiles[11] (Edinburgh, 1901): "It is more than probable that the majority of all oblique inguinal herniae in adolescents and young adults are congenital."

Oliver[12] (Newcastle, 1902): "Take what is known as rupture or hernia, which occurs with greater frequency in persons whose work obliges them to be long on their feet and who are exposed to sudden strains—the lifting of heavy weights, etc. What is said of it applies equally well to varicose veins in the legs. Both of these may be partially the result of position assumed by the individual when at work, or the result of strain that he is exposed to, and yet it would scarcely be right to make the occupation responsible for an affection, the result of an inherent weakness in the abdominal wall which allowed a portion of the intestine to protrude, giving rise to a rupture, or for an ill nourished condition of the walls of the veins in the legs whereby the blood vessels become distended and deformed."

Sheen[13] (Cardiff, Wales, 1904): "Under ordinary circumstances, the only explanation of the initial sudden appearance of a hernia lies in the existence of a preformed sac."

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9. Kingdon, J. A.: Tr. Med. Chir. Soc., 1864, p. 295.
10. Macready, Jonathan: A Treatise on Ruptures, London, 1893.
11. Stiles: Brit. M. J. **2**:599, 1901.
12. Oliver, Thomas: Dangerous Trades, New York, E. P. Dutton & Co., 1902.
13. Sheen, W.: Brit. M. J. **2**:60, 1904.

The conditions Sheen considers necessary for trauma to be regarded as a cause of hernia are:

"1. Trauma must be a sudden general contraction, compressing the abdominal contents, as in lifting a too heavy weight, or in resisting a blow, or possibly a general abdominal squeezing, as in a buffer injury. A localized blow on one part of the abdomen cannot cause a hernia.

"2. Must be small at first.

"3. Must appear immediately after the accident.

"4. Must be accompanied by acute pain and tenderness at the site of the hernia, and by the formation of a small lump there.

"5. Must be so acute as to compel the patient at once to leave his work and seek medical aid.

"The association of hernia with trauma is exceptional."

Chiene [14] (Edinburgh, 1907): "For practical surgical purposes, all oblique inguinal hernias are primarily due to a congenital or preformed sac."

Corner [15] (London, 1907) gives observations on 700 hernias in children. Thirty-four per cent. of these children had multiple hernias. (An indication of the importance of the congenital influence.)

Sheen [16] (Cardiff, 1909), in discussing the difficulties of a lay arbitrator, says, "In the midst of a mass of ill-understood technicalities following the line of least resistance and giving judgment to the workman in these hernia cases the post hoc, ergo propter hoc view is naturally considered the easiest one.

"The sudden first appearance of a hernia in the sense that it constitutes an accident arising from excessive strain is a very rare but not impossible event. Its sudden complete development in a pathological sense is improbable because the peritoneum cannot stretch suddenly to form the sac.

"The true traumatic hernia must be small at first. I believe that the sudden first appearance of a scrotal hernia is impossible. That the individual ceases work I believe is practically always true."

Deansley [17] (Wolverhampton, 1910): "There are conclusive reasons for believing that all, or almost all, inguinal hernias are congenital. There is absolutely no reason to suppose that oblique inguinal hernia ever arises without a preexisting sac formed by a patent funicular process."

Telford [18] (England, 1912) gives an able, academic discussion of the saccular theory, agreeing entirely with Murray, Russell, etc.

Roughton [19] (London, 1912): "I believe that all oblique inguinal hernia sacs in children and young adults are formed in this way [i. e. through a congenital sac] and that they are really never acquired."

Moffatt [20] (Cape Town, South Africa, 1912), draws the following conclusions:

"1. Hernia is a congenital defect.

"2. A repeated intra-abdominal pressure makes it obvious.

"3. The pressure is caused by the performance of physiological functions and muscular effort.

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14. Chiene: Brit. M. J. **2**:1389, 1907.
15. Corner, E. M.: Lancet **2**:78 (July 13) 1907.
16. Sheen, W.: Practitioner **83**:334-338, 1909.
17. Deansley: Brit. M. J. **1**:1487, 1903.
18. Telford: Med. Chron. **56**:17, 1912.
19. Roughton, E. W.: Lancet **1**:1534, 1912.
20. Moffatt, H. A.: Transvaal M. J. **8**:5-13, 1912-1913.

"4. In the small number of cases in which a wrench, a special effort or a strain is honestly thought to have caused the hernia, the effort or strain has only made it apparent, not in any way caused it."

Barnett [21] (Belfast, 1904), discussing the examination of an actual claim case says, "1. Was there a preexisting weakness, congenital or otherwise, which would markedly predispose to such an injury? If there was, then the accident was only an existing agent.

"2. Was there a preexisting congenital sac so slight as not to be noticed by the individual, but only requiring a slight strain to make it apparent? If so, the man cannot claim that the accident was the chief cause.

"3. Was there a preexisting hernia which the employee paid no attention to until an injury to the part drew his attention to it? Careful questioning and examination will reveal the truth."

Bennett [22] (Glasgow, 1917): "The position on examination seems to be that there is general acceptance of the view that the great majority of indirect hernias are of congenital origin—a view that is supported by embryological evidence, while the case for even a few of them being acquired rests on nothing more substantial than belief."

Handley [23] (London, 1918): "Murray and other surgeons have shown beyond doubt that the sac in nearly all inguinal hernias has existed from the beginning of life. It is a matter of chance, depending on the degree of intra-abdominal pressure, whether the preexisting sac is ever made evident by the descent into it of some of the abdominal contents."

Turner [24] (London, 1919) accepts the saccular theory of hernia and advocates an operative technic based entirely thereon. He says, "I consider that the congenital origin of the sac in the vast majority of inguinal herniae has been conclusively proved."

He notes that many British soldiers developed a hernia during training or in the field who also gave a history of hernia in infancy or childhood. The change from a sedentary to a military life evidently made these hernias, which were present in childhood, again become apparent to the person. He operated on many soldiers in whom, according to the history, hernia had been present only a few days or weeks and "never once found any bruising or other sign of trauma."

"The men (British soldiers) were practically all strong and well developed and otherwise healthy, and I strongly believe, in all these cases, that, though the hernia appeared to have been acquired, the sac was a congenital structure."

FRENCH LITERATURE

Bouradel (quoted by Berger [25]): "In the great majority of cases, hernia is not a sudden accident. It is an infirmity prepared by a congenital malformation."

Duchamps,[26] 1900: "Hernia prepared by a special disposition, congenital or acquired, appears often after a slight effort, which is its occasional cause and not its efficient cause. It should not be considered an accident of work and put as a charge on the employer."

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21. Barnett, Norman: Textbook of Surgery, London, Heinemann, 1914.
22. Bennett: Glasgow M. J. **88**:134 (Sept.) 1917.
23. Handley: Practitioner **100**:466 (June) 1918.
24. Turner: Inguinal Hernia, London, F. & A. Churchill, 1919.
25. Berger, P.: Rev. de chir. **33**:577-617, 1906.
26. Duchamps: Loire méd. **19**:258, 1900.

Jamin,[27] 1902: "There are very rare exceptions when hernia should be considered an accident of work."

Thiltges[28] (Belgium, 1903): "The great majority of hernias of force have been prepared for a long time and come on the occasion of work, not by work.

"The vaginal process is very often unobliterated, and a very little force, cough, or the least effort of any kind of work will force a piece of intestine into it. The hernia is only a late congenital hernia and does not deserve indemnity."

Solé,[29] 1904, stated that in 1895 the German Bureau of Insurance allowed thirty-two out of 400 hernia claims. Solé allows three classes of accidental hernia: (1) wounds of the abdominal wall; (2) massive contusions (run over accidents, etc.); (3) direct contusions.

Solé strongly insists that, in sudden hernia, pain must be "not vague, slight and moderate, but violent, like that produced by the blow of a whip, a pain which it is impossible to conceal and which can lead to syncope. Pain persists several days and the part remains tender.

"The protrusion of a hernia is not the same thing as its formation. It is simply the last phase of its development.

"All irreducible hernias are not recent."

Berger[25] (Paris, 1906) has published the most elaborate and complete monograph on hernia in connection with "accidents of labor" that I have seen. It covers about eighty pages of the *Revue de chirurgie* and should be carefully studied in the original. The work is based on carefully compiled statistics of more than 10,000 hernia cases in a large Paris clinic. Only a few extracts can be given to show the trend of Berger's authoritative teaching:

"We know that hernias, in the immense majority of cases, are not the result of an accident; that it is the accidental or professional effort which has revealed their existence. Hernias, in fact, result from a slow process which has for its real origin a constitutional defect of the abdominal wall, or a congenital weakness, consisting of a true malformation, or acquired and depending on a gradual weakening of the muscle and aponeurotic planes of the wall. This imperfection, congenital or acquired, localized in certain anatomical regions, shows itself by the existence of weak points where are concentrated the effects of abdominal pressure, necessarily increased by physiological, professional, accidental and pathological efforts. Under the influence of these causes, incessantly repeated, the weak point is forced to yield and a hernia is produced.

"This extrusion of viscera, unfolding the peritoneum in the abdominal wall and forming the hernial tract, is quite gradual. The hernia insinuates itself slowly in the thickness of the abdominal wall and has existed there a long time, perfectly recognizable to the eye and hand of one accustomed to such examinations. An accidental circumstance in determining a tension a little more painful than usual draws it to the attention of the patient."

Berger found in 117 subjects who noticed a hernia immediately after an accident or effort, and who held such to be the cause, that there were one or more additional hernias in ninety-six out of the 117 which had not been noticed.

"True hernias of force, those which are determined by an accident, a traumatism, an effort in a normal individual, are an exception—a very rare exception. The great majority of hernias which are referred to an accident

27. Jamin: Thèse de Paris, 1902.
28. Thiltges, N.: Presse méd. belge, Brux. **55**:786-791, 1903.
29. Solé: J. de méd. de Paris **16**:27, 1904.

have as the original cause a predisposition created by a weakening of the wall or by a congenital defect which has only hastened the appearance or more often only made manifest the existence of a hernia which already existed unperceived.

"The existence of a double hernia is incompatible with the idea of a hernia of force.

"Most oblique inguinal hernias which develop slowly, spontaneously, or under the influence of an accident have a congenital origin."

Berger gives very valuable suggestions for the detailed examination of claim cases, the detection and weighing of evidence of old hernias and predisposing conditions and valuable suggestions as to the weighing of the professional evidence in the case, and directions for making reports of practical utility to attorneys, etc. Other forms of hernia receive careful attention.

An editorial[30] in the *Journal de médecine de Paris*, 1907, gives the following extracts from French court decisions:

"When the hernia shows no characteristics of a hernia of force, i. e., suffering sharp, intolerable and prolonged, it is not an accident of work."

A lower French court and a higher court of appeal held against an applicant in whom a hernia appeared suddenly in the course of work, because the alleged cause represented no considerable effort. (In the French courts, an adequate force is apparently necessary.)

Another lower court, confirmed by a court of appeal, rejected a claim because the man continued his work after he felt the pains, showing how moderate the effort was and the insufficiency of the effort to determine a hernia.

Another French court says hernia appearing after an effort, normal in the course of labor, does not constitute an accident of labor.

Moreau[31] (Belgium, 1909): "A hernia of force is produced at once, at a given moment in a sound man under the influence of an effort, unusual, well determined and violent, with the accompaniment of sharp pain.

"The hernia of weakness appears unconsciously, little by little, under the influence of repeated efforts, constituting really a professional disease, or it shows itself following an ordinary effort without great pain."

Tierlinck,[32] 1909: "In hernia of force, pain is sharp and localized in the hernial orifice; there is malaise, weakness and often syncope. Continued work is impossible. Must see a doctor the same or the next day. Pain lasts several days.

"A strangulated hernia should not be considered due to a strain at work unless it is shown that the strain surpasses the normal limits for the particular work."

Poissonnier,[33] 1911: "If the worker is indisposed to such a degree that the hernia would have to appear eventually under the influence of the slightest effort, the court finds itself in the presence of the evolution of a disease and not an accident."

Reclus,[34] 1912: "Has the accident produced in the injured the severe general and local phenomena which are always, as far as clinical observation teaches us, the consequence of a traumatic hernia? If the facts are negative, your conscience is at rest.

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30. Editorial, J. de méd. de Paris **19**:53, 1907.
31. Moreau, C.: Med. d. accid. du travail, Paris **7**:140-145, 1909.
32. Tierlinck, A.: Ann. Soc. de méd. de Gand **89**:31-47, 1909.
33. Poissonnier, M.: J. d. sc. méd. de Lille **1**:529-537, 1911.
34. Reclus, P.: Rev. gén. de clin. et de thérap., Paris **26**:769-771, 1912.

"We know that traumatic hernia is characterized by a violent pain such that the injured cannot stand up. He falls and cannot rise without falling again. His face is anxious, covered with cold sweat. One finds, in the groin, a small swelling, very painful, irreducible and in which each movement, each pressure exaggerates the suffering. Often on the following day, one finds edema and traces of ecchymosis."

ITALIAN LITERATURE

Caccioppoli,[35] 1910: "The theory that a strain can produce a hernia is antiquated; hernia is a disease. A force, to cause a sudden hernia, must be sudden, abrupt and intense. Such a hernia produces such an intense and violent pain as to completely incapacitate any one for work."

(Further Italian literature on this subject has not been available.)

AMERICAN LITERATURE

Manley[36] (New York, 1892): "My own experience has led me to regard hernia of every description, as always, in every instance, being attributable to so-called predisposing causes solely and alone; to congenital antenatal conditions, the active cause being an incident only and nothing more, bearing about the same relation to the infirmity that a local injury does to a cancerous growth.

"I am able to say, without any qualification whatever, that hernia is never attributable to trauma alone unless the violence be applied by some hard, heavy, sharp pointed instrument, which either punctures or rends the abdominal wall; and that, when hernia appears after the application of an ordinary force, it can always be demonstrated that it had previously existed, the accident or injury being an incident only in its evolution."

After an exhaustive review of the literature then available Manley was "unable to find a single case of purely traumatic hernia recorded.

"I have never seen a case in which there was proof that a hernia was forced through any of the natural passages by inflicted violence among those who have been run over, who have been crushed in various ways, have fallen from a considerable height or sustained blows over any part of the abdomen.

"Physical force in itself can very seldom cause an abdominal hernia without at the same time inducing mortal changes.

"It may be stated with emphasis and certainty that the direct application of concussive force is never a primary cause of hernia.

"There is no evidence that ordinary bodily traumatism aggravates the herniated condition, except in those cases in which it is applied immediately over the herniated area.

"A more general knowledge of the above facts by the general mass of the profession should, while in no way interfering with the fullest measure of justice being meted out to the injured or crippled, nevertheless greatly restrain those who have a hernia from making it the sole cause for demanding extortionate sums or instituting criminal proceedings."

Marcy[37] (Boston, 1896): "The general opinion is that hernia is produced by some violent strain, or accident, for which in the general mind the term

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35. Caccioppoli: Med. ital. **8**:519, 1910.

36. Manley, T. H.: Herniae, Operative and Nonoperative, J. A. M. A. **19**:182 (Aug. 13) 1892; The Relation of Physical Violence to Hernial Protrusions Through the Abdominal Walls, ibid. **19**:387 (Oct. 1) 1892.

37. Marcy, H. O.: Operation for the Cure of Hernia Viewed from a Medico-legal Standpoint, J. A. M. A. **27**:979 (Nov. 7) 1896.

rupture is a synonym, that is, a sudden giving way of the parts involved. A superficial study of the case might lead one often to arrive at this conclusion. This is so exceptional that it represents a very minute fraction of the total."

Coley[38] (New York, 1902): "So far as known at present, traumatic herniae are produced or caused only by direct, heavy application of force, at the site where the force was applied."

Coley states that in 50,000 cases at the Hospital for Ruptured and Crippled in New York there were only four in which direct trauma was a probable factor, and even in these the proof was not absolute. "It is extremely doubtful if traumatism alone, without an open funicular process in the hernial canal, can ever produce a hernia."

Brown[39] (New York, 1904) reports the case of a jockey, 18 years old, whose horse reared and fell over backward on him. The patient immediately became very ill, with severe pain, vomiting and collapse. Dr. Brown saw him a few minutes later and found a typical, small strangulated inguinal hernia. This was reduced by taxis. There was no previous history of a hernia. Operation two weeks later revealed a small sac containing omentum. Operation and recovery were uneventful. (This case is abstracted somewhat fully, because it illustrates what any one would accept as a traumatic hernia. Even here, however, a direct blow by some part of the saddle and also the presence of a congenital sac are possible. Note that all the criteria of a traumatic hernia, such as excessive violence and immediate serious illness, are present.)

Morgan[40] (Augusta, Ga., 1904): "Traumatism is occasionally a true cause of hernia, but only by direct violence. One case in every 10,000 would be a liberal estimate for hernia as the result of injury.

"No concussive force, however severe, or simple increase of intra-abdominal pressure can ever be satisfactory as the primary and sole factor in the production of any form of abdominal hernia.

"The supposed sudden appearance of an acquired hernia is, in my opinion, always dependent on a mistaken observation."

His conclusions are:

"1. I think it is established by experience and a preponderance of testimony from our best authorities that indirect violence of any character can never be regarded as the cause of a hernia.

"2. Severe direct injury cannot be considered a causative factor, except where the muscle wall of the abdomen is ruptured by the injury, and the hernia appears at the point of injury.

"3. It is highly probable, if not absolutely sure, that in all cases of so-called traumatic hernia where ordinary force only is applied, the true cause will be found in congenital defects and not as a result of trauma."

Fowler[41] (Brooklyn, 1906): "The fact that the formation of the most important part of the hernia, namely the sac, occupies a period of time extending, in some instances, over many years, and is frequently a congenital condition, and the further fact that the occurrence of the protrusion results from a gradual traction and pushing forward of a certain isolated portion of the

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38. Coley: Progr. Med. **2**:40 (June) 1902.

39. Brown, F. T.: Ann. Surg. **39**:287-290, 1904.

40. Morgan, J. B.: Am. J. Surg. & Gynaec. **18**:26-28, 1904-1905.

41. Fowler, G. R.: Treatise on Surgery, Philadelphia, W. B. Saunders Company, 1906.

abdominal wall, should decide the question against the contention that hernia is to be considered as resulting from an accident, particularly as a number of such hernias depend upon peculiar local conditions, such as the existence of lipomas, etc.

"A hernia may make its first appearance after an injury. If, under these circumstances, it at once becomes strangulated, it may be deemed to be traumatic in origin."

Fowler limits traumatic hernias to those following operation.

Andrews[42] (Chicago, 1907): "I am very skeptical of the rôle of even severe injuries in producing inguinal or femoral hernias or any other form of hernia. I firmly believe that nine out of ten of the so-called acquired hernias of the railroad man, or any man in laborious occupation, after some fall or sudden jump from a high place or some crushing force—I do believe that the patient in that case either already had the hernia and did not know it or else that it was preexistent and he merely had an increase in size of it.

"There is often a time in the history of a hernia when even a physician does not determine that it is present. After some strain, the patient will finally discover that he has a small inguinal lump or the physician will perhaps discover it. This does not prove, however, that it has just come into existence."

Butte[43] (Philadelphia, 1907): "The extrusion of bowel or omentum and its entrance into the sac are but the last of a long series of antecedent and preparatory changes. Repeated muscular effort forms the way for the actual protrusion of the hernia. The last effort is the culminating etiological factor—the straw that broke the camel's back."

Eccles,[44] 1908: "In the majority of cases, a hernia is of gradual and slow formation, and this without any tearing or breaking of tissue, such as is clearly indicated in the use of the word rupture.

"It is decidedly rare for a hernia to be formed suddenly, and the very fact that the applicant for compensation gives the history of a rapid development of his protrusion should of itself be a cause of suspicion.

"A person may aver that he has developed a protrusion not suddenly but at a period which is remote from the date of the accident, believing it to be caused by it. . . . If it is in one of the usual positions for a protrusion, the inguinal, femoral or umbilical region, it is highly probable that the accident had little or no part in its causation."

Outten[45] (St. Louis, 1908), who probably had a larger experience as a railroad surgeon than any other man, says, "Any surgeon who has made a careful study of the surgery of violence, that is, railway and allied injuries, must and will come to the conclusion that traumatic hernia is so extremely uncommon as to leave doubt as to its verity in almost every case.

"Sudden muscular effort can never be the cause of rupture. I have never seen but one case of inguinal rupture in which the rupture was seemingly the product of an immediate injury.

"The consensus of opinion with the great majority of authorities on this subject is against the possibility of the occurrence of hernia as a result of trauma.

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42. Andrews, E. W.: Railway Surg. J. **13**:169 (Jan.) 1907.
43. Butte, H. J.: New York M. J. **86**:739-742, 1907.
44. Eccles: Hernia, New York, William Wood & Co., 1908.
45. Outten, W. B.: Interstate M. J. **15**:334-349, 1908.

"Medicolegally, then, the existence of traumatic hernia has not been proven."

Coley[46] (New York, 1909): "Hernia is a disease rather than an accident. . . . The congenital defect, then, is the main cause of a hernia, while the immediate or exciting cause plays but a minor rôle."

Harbaugh,[47] 1909: "The symptoms of a true traumatic hernia are easily recognized and differentiated from hernia which passes into a sac which has been in the process of construction for a more or less long period of time."

Allport[48] (Chicago, 1909): "I am not a believer in traumatic hernias. Ecchymosis, boggy swelling, local tenderness and congestion, mild febrile movement, etc., should just as certainly accompany genuine violence in the hernial region as in any other part of the body."

Magruder[49] (Baltimore, 1910): "In most instances in which hernia is supposed to have been acquired as the direct result of an injury or a strain, careful investigation will prove that it existed before, but was either not recognized or, being rendered larger by increased strain, was brought suddenly to the individual's notice.

"Localized blows over the abdomen, owing to the fact that they do not cause compression, cannot give rise to hernia.

"From a study of reported cases and a general review of the literature, it is fair to conclude that injury is never the direct and only cause of inguinal or femoral hernia but may be the means of increasing the size of, or calling attention to the presence of, a hernia which already exists. In order that hernia can follow as the direct and only result of an injury, independent of previous weakness or congenital sac, some very severe and penetrating wound to the abdomen must take place."

Wood[50] (Philadelphia, 1910) agrees entirely with Russell and says, "Trauma may be an exciting cause of hernia in rare instances but only provided a sac already exists. True traumatic hernia is of very rare occurrence.

"It is impossible for a hernial sac to form instantly, under ordinary circumstances."

Hessert[51] (Chicago, 1910): "A close study of this region at operation and examination of the sacs in situ and after removal forces upon one the conclusion that many of these cases were of congenital origin. The chief etiological factor underlying the development of oblique inguinal hernia in fully three fourths of the cases can be traced to the preexistence of a congenital sac, the result of faulty closure of a part or the whole of the vaginal process. This proposition has been sustained in the last 100 operations in the author's practice."

He reports studies on 503 infants, with the following result: vaginal process open on both sides in 26.6 per cent.; right side open in 12.7 per cent.; left side open in 5.1 per cent., or 44.4 per cent. of infants have an open process on one or both sides.

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46. Coley, in Keen, W. W., and Da Costa, J. C.: Surgery: Its Principles and Practice, Philadelphia, W. B. Saunders Company, 1909.

47. Harbaugh, C. H.: Med. Exam. & Pract. **20**:16-19, 1909.

48. Allport, W. H.: Internat. J. S. **22**:162-167, 1909.

49. Magruder, W. E.: Claims Arising from the End-Results of Injury, Baltimore, 1910.

50. Wood, A. C.: Month. Cycl. & M. Bull. **3**:11, 1910.

51. Hessert, W.: Surg., Gynec. & Obst. **10**:252-256, 1910; discussion, pp. 327-329.

Bevan[52] (Chicago, 1910) says, in a discussion of Hessert's paper, "I am quite of the opinion that the view taken by Russell and Dr. Hessert and others is quite correct, that the preformed sac is the most important factor in both femoral and inguinal hernias."

Connell[53] (Oshkosh, Wis., 1910), in discussing Hessert's paper, says, "It reinforces my opinion that practically all oblique inguinal hernias are of congenital origin."

In discussing Pillon's paper, to be noted later, Connell says, "The occurrence of true traumatic hernia is unusual. I have never seen such a case and I would say that, if it does occur, it must be with such a severe injury that the hernia will probably be of small moment."

Foltz[54] (Fort Smith, Ark., 1910) says, "Accidental direct traumatic herniae are curiosities."

McCandless[55] (St. Louis, 1910) says, "Nearly all oblique hernias are of congenital type and depend more on the preexisting condition than upon any present energy for their production."

Bendixen[56] (Davenport, Ia., 1910) says, "No hernia should be considered an industrial accident with the exception of the true traumatic variety, i. e., the direct result of external violence.

"No employer should be held responsible for an anatomic malformation of his employee and should not under any circumstances be made to pay damages for said defect."

MacLennan[57] (Chicago, 1910) gives an elaborate and convincing proof of the saccular theory of hernia and says that it "goes a long way to prove that the essential factor in the production of a hernia is the presence of a pre-existing sac."

He calls attention to the fact that, if one examines a patient with recurrent hernia at a time when it is reduced, it is impossible to force intestine or omentum into the sac by any degree of pressure of the surgeon's hands on the abdomen.

Pember and Nuzum[58] (Janesville, Wis., 1910), illustrating the point just mentioned by MacLennan, report the case of a laborer, 55 years old, whose abdomen was severely crushed between a boat and some fixed object. The compression ruptured the intestine, and he died. He had an old hernia, but nothing was forced into the sac by this severe crush.

These authors have performed an elaborate series of experiments on cats; and, as a result of this and their clinical experience, say, "In true traumatic hernia, you have the history of a most severe injury and the profound shock that always accompanies it, the protruding mass or swelling, and often ruptured internal viscera. . . . The indications are so plain that he who runs may read.

"Traumatic hernia is not likely to be produced by a blow which is short of lethal, unless a punctured wound is produced.

"A blow which is sufficiently severe to produce hernia would be certain to do sufficient violence to other abdominal organs to prove fatal."

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52. Bevan, A. D.: Surg. Gynec. & Obst. **10**:328, 1910.
53. Connell, F. G.: Surg. Gynec. & Obst. **10**:327, 1910.
54. Foltz: Railway Surg. J. **17**:337, 1910-1911.
55. McCandless, W. A.: Railway Surg. J. **17**:333-337, 1910-1911.
56. Bendixen, P. A.: Railway Surg. J. **17**:330-333, 1910-1911.
57. MacLennan, A.: Surg., Gynec. & Obst. **10**:57-59, 1910.
58. Pember and Nuzum: Wisconsin M. J. **9**:663-673, 1910-1911.

Reineking[59] (Milwaukee, 1910), discussing Pember and Nuzum's paper, says, "So far as true traumatic inguinal, femoral or umbilical hernia is concerned, I have never seen a case.

"The diagnosis of traumatic hernia should not be made unless it can be based on the following conditions: If seen soon after the occurrence of the injury, there should be pronounced local symptoms. If seen later, the diagnosis should not be made unless the surgeon is previously familiar with the patient's condition before the injury for the reason that, although the patient may be perfectly honest, a partial hernia may have been present without his knowing it.

"I have never seen a case which I could consistently call traumatic hernia at one of the hernial openings."

Harrington[60] (Milwaukee, 1910), discussing Pember and Nuzum's paper, says, "The first and essential principle we should get in mind is that the presence of a hernia following force is not sufficient to bring it under the classification of traumatic hernia.

"You cannot get a traumatic hernia without severe shock and without the symptoms of an unusual and violent injury."

Corwin[61] (Pueblo, Colo., 1910) writes a convincing paper on this subject, and quotes Charles Mayo, as follows: "It is extremely doubtful if traumatism alone, without the funicular process in the inguinal canal, can ever produce a hernia. The trend of surgical opinion is rapidly growing in the direction of considering practically all cases of hernia to be due to a preformed sac of congenital origin, which forms the great predisposing cause for hernia."

Corwin also quotes A. F. Jonas, as follows: "I believe that no man will have an inguinal hernia if his vaginal process is completely obliterated."

Frank[62] (Kentucky, 1911) says, "If we have a peritoneal covering, that in itself is absolute evidence that we have not a traumatic hernia."

Bloch[63] (Louisville, Ky., 1911) draws the following conclusions:

"1. Traumatic hernia is very uncommon.

"2. The occurrence of traumatic hernia is impossible without a predisposing condition.

"3. Traumatic hernia always presents unmistakable symptoms."

Dugan[64] (Kentucky, 1911) in discussing Bloch's paper, says, "Any claim of traumatic hernia which is not accompanied by intense pain coming on suddenly is not well grounded . . . most with intense shock."

Corwin[65] (Pueblo, Colo., 1911) refers to some experiments of his own, showing the strength of the inguinal canal, and says, "For a viscus to force itself through a healthy abdominal wall by muscular contraction or jar seems well nigh impossible."

He believes that, in an unsound body, an accidental hernia may occur with a readiness depending on the degree of the abnormality, but "accidental hernia in a sound body is improbable."

Pilon,[66] 1911: "A patient who complains of hernia, several days after the accident, had a hernia before the accident occurred." (Connell's discussion of this paper is noted above.)

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59. Reineking, H.: Wisconsin M. J. **9**:671, 1910-1911.
60. Harrington: Wisconsin M. J. **9**:670, 1910-1911.
61. Corwin, R. W.: Colorado Med. **7**:283-289, 1910.
62. Frank, Louis: Kentucky M. J. (Jan. 15) 1911.
63. Bloch, O. E.: Kentucky M. J. **9**:84-88, 1911.
64. Dugan: Kentucky M. J. :86 (Jan. 15) 1911.
65. Corwin, R. W.: Am. J. Surg. **25**:93-95, 1911.
66. Pilon, P. C.: Railway S. J. **18**:276-282, 1911-1912.

Fort[67] (Louisville, 1911): "I do not believe that there is any such thing as traumatic hernia by indirect violence."

Miller[68] (Villa Grove, Ill., 1911): "I do not think we have such a thing as traumatic hernia. A traumatism which has sufficient force to produce an inguinal hernia in a ring that is normal in its size and without inherent weakness would inflict a fatal injury."

Moschowitz[69] (New York, 1911) shows how an inguinal hernia really can be traumatic. He relates the case of a young Russian who, to escape army service, was taken by his friends and laid on the floor. One man sat on his head, another man ran a finger into the groin. This caused so much pain that the subject fainted. He was taken home and told to take snuff and drink yeast to make him vomit. He sneezed and vomited all night and the next morning had a hernia. It is interesting to note that the army surgeons suspected some such performance and accepted this young man just the same.

The same author, in 1915, presented a very convincing scientific proof of the importance of the preformed sac and the rarity of traumatic hernia. This paper should be read in the original. Moschowitz says, "My aim in writing this paper is to prove a fact at which I arrived after many years of careful study, namely, that traumatic hernia does not exist." He then makes an exception to this statement to include only postoperative hernias and those which are due to direct blows of more or less sharp instruments, and those in which there is a distinct laceration of the tissues of the abdominal wall.

Plummer[70] (Chicago, 1915), who has had, for many years, a large experience as chief surgeon of the Rock Island Railway, publishes an important paper on this subject, which should be read in the original. He states that he has seen many cases of severe injuries to the abdomen in people who have been run over by automobiles, injured in railroad wrecks, etc. He has seen all kinds of ruptures of the abdominal viscera, but he has never seen an inguinal hernia follow such an injury, even in the severest cases. He says, "A single strain can never be the cause of a hernia. Even if predisposing causes are present, a hernia cannot be forced down as the result of a severe strain without stretching and lacerating the surrounding tissue so as to cause great pain as well as edema and ecchymosis. The patient will at once cease his occupation and call attention to the fact that he is injured.

"Cases where the employer should be held liable are rare exceptions."

Duff[71] (Chicago, 1915): "Ninety-eight per cent. of all hernias do not come under the Workmen's Compensation Act."

Levings[72] (Wisconsin, 1915): "Hernia, to be classed as one of effort or due to traumatism, must occur for the first time during unusual effort or traumatism. The hernia must be small, tense, painful and disabling, in other words strangulated."

Brickner[73] (New York, 1915): "Herniae through umbilical, inguinal or femoral canals are never traumatic, we believe (except, to be quite exact, in such rare instances in which a penetrating injury actually occurred to these canals).

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67. Fort, F. T.: Railway Surg. J. **18**:412-419, 1911-1912.
68. Miller, J. M.: Railway Surg. J. **18**:417, 1911-1912.
69. Moschowitz, A. V.: Ann. Surg. **54**:265, 1911.
70. Plummer: Chicago M. Rec. **37**:307, 1915.
71. Duff, R. R.: Illinois M. J. **27**:184-188, 1915.
72. Levings, A. H.: Wisconsin M. J. **14**:273-276, 1915.
73. Brickner: Am. J. Surg. **29**:223 (June) 1915.

"Herniae discovered at one of those sites were present before the strain, fall or blow, potentially, or small, or, most often, fully developed but perhaps unnoticed."

Salmon[74] (Ashland, Ky., 1915) presented an able discussion of this subject at the meeting of the Chesapeake and Ohio Railway. Dr. George Ben Johnson of Virginia offered a resolution which was unanimously adopted at this meeting, endorsing Dr. Salmon's paper and expressing the unanimous opinion of the association that hernia is never traumatic.

Smith[75] (Randsburg, Calif., 1916) quotes a personal letter from the California Industrial Accident Commission, as follows: "The rupture must occur at once following an unexpected blow, fall or strain greater than the individual meets in the regular run of his occupation. The production of the rupture must be accompanied by pain that disables the patient at once and continuously, and makes immediate recourse to the surgeon imperative. The patient must, furthermore, furnish clear evidence of the nonexistence of the hernia previous to the alleged accident."

Locher[76] (Baltimore, 1916): "The sac is the terminal result of a gradual process and not the result of a single sudden strain or effort."

Bacon[77] (Miami, Ariz., 1917) relates an interesting phase of fourteen years' experience in a mining community. From 1903 to 1910, he saw no case of hernia in which accident was claimed as a cause. From 1910 to 1914, he saw one case in which recent injury was claimed. In 1915 the Workmen's Compensation Law was passed, and in this year six persons claimed that a hernia was due to a recent injury. In 1916 there were ten such cases, and in 1917 there were seventeen such cases up to September 1.

Da Costa[78] (Philadelphia, 1918): "In true traumatic hernia, there are violent pain, collapse, vomiting, inability to walk or stand, and the mass does not return to the belly on recumbency, but must be reduced by taxis or operation."

Blake[79] (Boston, 1919), discussing a case of hernia claimed to have been contracted in playing baseball, says, "I doubt very much if a hernia is caused from sliding to first base or a sprint around the bases unless there was a previously large ring, probably a potential hernial sac."

Mock[80] (Chicago, 1919) gives an able discussion of this question in his valuable textbook. On business and philanthropic grounds, he takes a broad view of the advisability of caring for the afflicted persons, although he apparently accepts the current medical opinion concerning the influence of a congenital sac, etc.

Lauffer[81] (Pittsburgh, 1919): "Hernia in a preformed sac is a disease, irrespective of the circumstances accompanying the first appearance of a mass in the groin. Peritoneum cannot be pushed out to form a sac by any single impulse.

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74. Salmon, J. M.: Virginia M. Semimonth. **20**:290-292, 1915-1916.

75. Smith, W. B.: Calif. State J. M. **14**:351, 1916.

76. Locher: Spectator (March 23) 1916.

77. Bacon, J. E.: Southeastern Med. **1**:9-12 (Sept.) 1917.

78. Da Costa, J. C.: Modern Surgery, Philadelphia, W. B. Saunders Company, 1918, p. 1275.

79. Blake, J. B.: Internat. Clin. **2**:90, 1918.

80. Mock, H. E.: Industrial Medicine and Surgery, Philadelphia, W. B. Saunders Company, 1919.

81. Lauffer, C. A.: J. Indust. Hygiene **1**:177-182 (Aug.) 1919.

"Acquired hernia as encountered in industries is likewise a gradual process, and, while its discovery may cause a surprise to the patient, it has really been a longer time on the way than he knows of.

"Noted general and leading industrial surgeons are unanimous in their opinion that a hernia is to be classified as a disease, except the rare cases of general traumatic hernia.

"Over 4,000 hernias have been compensated in Pennsylvania [in the first three years of the compensation law], or more than the real cases of traumatic hernia that have occurred in the western hemisphere since Columbus."

Colcord[82] (Clairtown, Pa., 1919): "The wrong idea of hernia, promulgated by English surgeons and English courts of the nineteenth century and continued by our own courts and compensation boards, has been productive of much injustice to employers of labor.

"The force which produces traumatic hernia is tremendous, far beyond the ordinary strains of labor.

"To have a real traumatic hernia we should have: (1) direct violence at the point of hernia, causing such severe injury to the abdominal wall as to produce a hernia at once or in a few days; (2) indirect violence, causing enormous increase in intra-abdominal pressure far out of all proportion to the lifting, straining, etc., of ordinary labor.

"A hernia first complained of by the patient after an accident or a heavy lift does not prove that the accident caused the hernia. It discovered it to the patient, if honest, or if dishonest it afforded him an opportunity to sell an old hernia to his employers."

Saunders[83] (Fort Worth, Tex., 1918): "It is inconceivable that the sac of a hernia can be formed by one violent act driving the abdominal organs against the peritoneum without breaking it wide open. . . . Such a condition would be followed by signs and symptoms, both local and general, that would be unmistakable.

"Hernia is not due to traumatism or injury, but is a perfectly natural occurrence that may develop in any individual not made proof against it, or immune to it, by a perfect anatomical organism.

"If he has a preformed sac, the only sure way an individual can avoid developing a hernia sometime is to die before it shows up."

Patterson[84] (Harrisburg, 1918), as chief of the Division of Industrial Hygiene and Engineering, Pennsylvania Department of Labor and Industry, has had unusual facilities for a broad observation of this question and has published a very able article. He has given a very interesting review showing the attitudes of various compensation boards on the question of hernia and clearly shows how foolishly different their rulings are. His own opinion is that "hernia in practically every case (except those very rare cases where a traumatism causes a solution of continuity of the abdominal wall) is the result of a prenatal anatomical defect and should be classed as a disease and not as an accident."

Patterson considers that "all other cases will be considered as either congenital or of slow development and not compensable, being a disease rather than an accidental injury, unless conclusive proof is offered that the hernia was immediately caused by such sudden effort or severe strain that:

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82. Colcord: Internat. J. S. (Sept.) 1919.

83. Saunders, B.: Texas State J. M. **14**:164-166 (Aug.) 1918-1919.

84. Patterson, F. D.: Penn. M. J. **22**:633-642 (July) 1919.

"1. The descent of the hernia immediately followed the cause.

"2. That there was severe pain in the hernial region.

"3. That there was such prostration that the employee was compelled to cease work immediately.

"4. That the above symptoms were of such severity that the same were noticed by the claimant and communicated to the employer within twenty-four hours after the occurrence of the hernia.

"5. That there was such physical distress that the attendance of a licensed physician was required within twenty-four hours after the occurrence of the hernia."

(The foregoing five criteria have been adopted by the Legislature of the State of New Jersey and made statute law. I would add one more item which I consider to be very important, namely, that the strain or whatever force it may be must be adequate.)

The physicians constituting the Conference of the Industrial Physicians and Surgeons of Pennsylvania, at the meeting addressed by Patterson, unanimously adopted his views and recommended to the state legislature a proposed law embodying them. This bill, for reasons unknown, was not passed.

Sellenings[85] (New York, 1920): "Any traumatism sufficiently severe to produce a hernia acutely should, of necessity, be accompanied by shock, but shock is conspicuously not recorded in these traumatic hernias. Indeed, the claimants in these cases quite generally continue their daily pursuits until seized by the inspiration of cause and effect.

"The sudden first appearance of inguinal hernia in the sense that it constitutes an accident is an impossible event. The peritoneum cannot stretch instantly, but it has great power to stretch gradually. Local blows cannot cause a hernia; they may cause a subcutaneous laceration.

"In academic discussions of hernia, apart from the medical-legal aspect, there seems to be a uniform acceptance of the congenital origin of hernia.

"Hernia is not the result of immediate sudden effort, it is always of slow formation, and very few individuals are aware of its oncoming. Its development is gradual and almost painless.

"A hernia is a matter of scientific fact and not one of court interpretation."

Hopkins[86] (Chicago, 1921): "Personally, the more we see of these cases of traumatic hernia and of so-called traumatic hernia, with the alleged ease of their acquirement, and with the absence of symptoms that should have presented at the time the hernia is said to have been received, the more firm is our conviction that the actual occurrence of true traumatic hernia, in the average individual who comes before us, is rarely, if ever, seen.

"No doubt there are cases of true traumatic hernia, but in railroad surgery in particular, which calls for the care of patients who have received severe falls or squeezings through the abdomen and pelvis, producing extreme intra-abdominal pressure, sufficient to cause rupture of the bladder, kidney, liver, intestines, or to crush the pelvis, why is it that inguinal hernia is never found as a concomitant, unless the injuries were probably of sufficient severity to cause death?"

Hopkins notices that in his railway experience employees who are examined before employment present less than 1 per cent. of claims for traumatic hernia. Employees in classes not examined, which include largely the Southern Euro-

85. Sellenings, A. E.: New York M. J. **111**:713-717 (April 24) 1920.

86. Hopkins, C. W.: Internat. J. S. **34**:14-19, 1921.

peans, present more than 99 per cent. of the claims for traumatic hernia. The first examination of 186 men showed forty-eight with either single or double hernias of long standing.

Moorhead[87] (New York, 1921): "Can a single act of violence cause a hernia?

"No, unless it has caused a severing of the overlying muscular and fascial protectives.

"No single isolated act of violence causes a hernia unless the overlying parts have been lacerated.

"No single act of violence aggravates a hernia unless that violence produced intra-abdominal pressure and immediate onset of symptoms."

Burke[88] (Petersburg, Va., 1921): "The internal abdominal ring cannot, by any act of violence, be stretched sufficiently to permit protrusion and escape of abdominal contents, and at the same time the inguinal canal cannot be enlarged so suddenly as to allow this to descend into the scrotum. Common sense alone will tell us that the parts would be torn, with resulting hemorrhage, shock, etc., and probably death, if such an accident could occur.

"No hernia was ever caused by trauma."

Black[89] (Spartanburg, S. C., 1921): "Traumatic hernia is so rare as to constitute a surgical curiosity, yet it does occur. It is characterized by great pain, collapse, nausea and vomiting. There is a distinct mass, exquisitely tender, which does not disappear on reclining but may be reduced by taxis, or operation."

Duncan[90] (Omaha, 1921): "We must always keep in mind that the particular act or circumstance to which the hernia is attributed may have only enlarged a preexisting hernia sufficiently to make it noticeable to the patient."

He reports that in six out of his own twenty-two cases of double hernia the patient was aware of hernia only on one side.

Coley, Leigh, Walker and Hopkins,[91] of the United States and Hutchison, of Montreal, 1922, have published the most recent, as well as the most authoritative, American contribution. These surgeons have constituted a committee on traumatic and industrial hernia for the medical section of the American Railway Association. Their report should be read in full. A few quotations, however, will serve to indicate their general attitude: "The all-important cause of hernia of all varieties is the presence of a preformed sac of peritoneum.

"Unfortunately, courts and juries and compensation laws here and abroad have not kept pace with the developments of surgery.

"Russell maintains that an acquired hernia does not exist, and recognized authorities on hernia have come to agree with Russell's conclusions.

"Hernia is practically always due, first to the presence of a preformed sac or open pouch of peritoneum which, in the inguinal variety, follows the testis in its descent into the scrotum, which pouch has failed to close in the normal way; and second, to the presence of structural weakness in the neighborhood of the hernial orifices due to poorly developed muscles or fascia. Given these

87. Moorhead: S. Clinics N. America **1**:1573 (Dec.) 1921.
88. Burke, J. M.: Internat. J. S. (Feb.) 1921.
89. Black, S. O.: South. M. J. **14**:625-629 (Aug.) 1921.
90. Duncan, J. W.: Nebraska M. J. **6**:235-243 (Aug.) 1921.
91. Coley, Leigh, Walker, Hopkins & Hutchison: Ann. Surg. **75**:467 (April) 1922.

all-important anatomical causes, which are in themselves sufficient in many cases to constitute a potential hernia, the actual hernia may develop by reason of a great variety of exciting causes; among these may be mentioned the daily increase in intra-abdominal pressure incident to the ordinary routine of life, e. g., straining at stool, coughing, sneezing, lifting, etc. The main point that cannot be emphasized too strongly is that the hernia is never the result of a single strain or single increase in intra-abdominal pressure due to any of the causes mentioned; on the other hand, it is the cumulative effect of a great number of strains spread over a considerable period of time. In nearly all cases, hernia is of gradual onset, and is rarely accompanied by pain, and most frequently remains unnoticed until it has reached a considerable size or until some accident or strain, by slightly increasing the contents of the hernia sac, causes it to be noticed for the first time. Hence, the accident or strain is usually the occasion which first attracts the attention to a hernia long present but hitherto undiscovered. It has been a matter of almost daily observation at the Hospital for Ruptured and Crippled to find a patient applying for a truss or for operation for a hernia on one side, when careful examination discloses that he has a hernia on the other side, almost, if not quite, as large as that for which he applied for treatment. The size of the hernia and the character of the sac as determined by operation prove beyond question that this hernia existed for a long period and was quite unrecognized by the patient. Hence it is true that, in many cases, a person who claims that his hernia is due to an accident or any injury may sincerely believe this to be the fact, because he was unaware of the presence of a swelling prior to the accident, although it had really existed for months or years before. . . . In all our experience we have never seen a single case in which there was any sound basis for the claim that the accident or injury was the cause of the hernia.

"Convince the commissions and the courts of the well-established surgical fact that hernia is a disease and not the result of an accident.

"Any case of hernia developing in the course of duty, incident to the man's daily work, should be treated as a disease due to special anatomical weakness on the part of the individual, for which the company is in no way responsible."

Brickner[92] (New York, 1922): "If those who are familiar with the anatomy of hernias stop to think of the matter, they must recognize that a fully developed hernia cannot possibly be produced by any single blow or effort causing increased intra-abdominal pressure. The accumulating literature of recent years shows that the surgeons, especially, have been thinking, and that the belief that hernias have their origin in strains and injuries is being gradually abandoned. It is interesting to note, too, in occasional reports of decisions by courts and workmen's compensation boards, that there is, correspondingly, a growing recognition of hernias as anatomical defects rather than as consequences of traumata."

GERMAN LITERATURE

Grasser,[93] 1900: "It is the consensus of opinion among those who have given the subject most careful attention that the sudden complete development of a hernia is a very rare occurrence, so rare that it is of hardly any significance from a practical standpoint."

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92. Brickner: Herniae and Accident Claims, Am. J. Surg. **36**:148 (June) 1922.

93. Grasser: Handbook of Practical Surgery **20**, 1900.

Golebiewski[94] (Berlin, 1900, translated by Bailey), quotes from the German Manual of Accident Insurance: "To justify the payment of insurance, the hernia must be developed suddenly and be accompanied by intense pain. . . . The sudden development of a hernia invariably causes pain of a character so intense as to be almost unbearable, to which the affected individual involuntarily gives expression, and which obliges him to interrupt his work and to consult a physician at once. . . . If no proof of this kind is forthcoming, it is to be presumed that the work during the performance of which the descent of the hernia occurs furnishes the occasion of the same but does not act as its cause, and is, therefore, to be regarded as the cause leading to the discovery of the condition, not as the cause of the hernia itself."

Sultan[95] (Göttingen, 1902, edited by Coley): "It may be emphasized that complete protrusion of the peritoneum into a hernial sac never occurs from a single augmentation of intra-abdominal tension, no matter how great it may be. Such a protrusion always occurs slowly, as the result of the repeated effect of some of the influences just mentioned.

"If a hernial tumor suddenly makes its appearance during a marked increase of intra-abdominal tension in an individual who has previously presented no signs of hernia, we may be sure that the hernial sac was either congenital or gradually formed during some period of extra-uterine life.

"A hernia, complete in all its parts, can never arise at the moment of an accident or by a single augmentation of intra-abdominal tension, be it ever so great. If the hernia appears at the time of the accident, we may certainly suppose that the hernial sac either was congenital or gradually formed in the manner already described."

Von Bergman,[96] 1904: The article on hernia in this system is by Grasser, who confirms the views previously quoted and says, "Only a very small percentage of hernias are the immediate result of accident. The early stages of hernia are overlooked by the majority of individuals, and the patients are not aware of the condition until the hernia is perfectly evident to everybody.

"About one out of every fifteen males develops a hernia. In operative cases, about 30 per cent. show a patent vaginal process [that is, a typical congenital type of sac (?)]."

Berner,[97] 1904: "A sudden development of inguinal hernia is theoretically impossible and has not been demonstrated practically."

Aderholdt and Silberstein,[98] 1908: "We believe that hernias due to over-exertion are to be relegated to the realm of fancy. In this we are supported by so experienced a man in the line of hernias as Goertz, who believes that the only cause of traumatic hernia is an actual accident and who no longer acknowledges over-exertion while working as a cause."

Krymow,[99] 1910: "In the inguinal region, oblique hernias are always of natural origin, but direct hernias may be artificial."

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94. Golebiewski, translated by Bailey, Pearce: Diseases Caused by Accidents, 1900.

95. Sultan, George: Atlas and Epitome of Abdominal Hernias, edited by Coley, 1902.

96. Graser in Von Bergman: System of Practical Surgery, 1904.

97. Berner: Aerztl. Sachverst.-Ztg., Berlin **10**:472, 1904.

98. Alderholdt and Silberstein: Ztschr. f. Orthop. Chir. **20**:1-47, 1908.

99. Krymow: Arch. f. klin. Chir. **91**:745, 1910.

Schlender,[100] 1910: "In every traumatic hernia, one is able to prove the existence of a bodily injury which consists of wounds, or strangulation, or both.

"Accidental hernias may depend on the existence of congenital tendencies or pathological circumstances. Indemnities are not necessary in these cases."

Dreesman,[101] 1911: "A true hernia, i. e., a hernial sac and its contents without signs of strangulation, cannot be brought about by a single injury."

Scharezky,[102] 1913: "Without a more or less open processus vaginalis, no protrusion of the peritoneum can take place in the region of the internal inguinal ring from which a hernial sac would eventually be formed."

Kolb,[103] 1915: "Demands for payment of accident compensation on account of sudden exacerbation of preexisting hernias . . . are frequently and justly refused, because any hernia is naturally liable to develop and enlarge further and because such enlargement caused by work and at work must be regarded as an occupational disease."

Schepelmann,[104] after describing the inguinal canal, says, "In such a canal, either a congenital or an acquired hernial sac can occur, but never because of a single trauma, only by means of long-continued pressure, except if strangulation took place."

This writer quotes from the Imperial Insurance Bureau, as follows, "Whether the first appearance of hernia under the influence of an industrial accident is liable to compensation must be accompanied by proof of: (1) no previous hernia; (2) strong peritoneal inflammation, vomiting, insufferable pain, incapacity for work, eventual collapse; (3) the injured person must visit a doctor within the first three days; (4) the accident must have occurred in the performance of work unusually heavy for the injured one, and even too heavy for a healthy person."

IV. THE PRACTICAL APPLICATION OF THE SACCULAR THEORY

The foregoing review of the medical literature as noted covers my personal review of every title bearing on this phase of hernia in the French and English literature, and also of abstracts made by the American Institute of Medicine of all the Italian and German titles available in the New York libraries. This has included more than 200 articles in all. It is a rather convincing argument that every writer has agreed more or less in complete detail with the opinions directly quoted. Not a single article was found taking issue with any of the principles, with the single exception of a brief note by Keith, a British embryologist, who differs with Russell in a minor way concerning the embryology of the femoral canal.

It would seem that this review of the literature without further recapitulation should be convincing evidence that the real connection between oblique inguinal hernia and trauma, accident or the compensation laws is a very limited one. Even the most skeptical should agree

100. Schlender: Beitr. z. klin. Chir. **66**:488, 1910.
101. Dreesman: Ztschr. f. ärztl. Fortbild. **8**:221, 1911.
102. Scharezky: Centralbl. f. Chir. **40**:1918, 1913.
103. Kolb: Fortschr. d. med. **32**:1045, 1059 (July 8 and 22) 1915.
104. Schepelmann: Med. Klin. **5**:911 (Aug. 15) 1915.

that it shows that the 4,000 cases in three years in Pennsylvania represent an absurdly grotesque situation.

There can be no ground whatever for denying that a congenital sac is present in practically every case of oblique inguinal hernia, and that this is the great and efficient predisposing cause of this type of hernia, and, of its own account, without any essential exciting cause, is responsible for the natural production of most hernias. Medical opinion is unanimous on this as a scientific point. It is founded on incontrovertible evidence of dissections, operations and clinical observation.

However, from the standpoint of workmen's compensation, the issue is different. Even if a man is the carrier of a congenital sac, it is freely admitted that he may go through life without an actual hernia developing in it. When such a man can definitely establish that no hernia was present before, but that, on a certain occasion, a great and adequate force has produced an actual palpable hernial tumor, he has been changed from a man who was, to all intents, in a state of normal capacity for work, to one who now has a disability requiring a serious operation for its cure and for whom, without a cure, hard manual labor may be difficult, dangerous or impossible. A part which, though weak from birth, has not been a source of disability has now become such a source, to at least some extent. The workman is in little, if any, different situation from a man who since birth has had a vision of 20/40, good enough for work, but who as the result of an injury has had a change in vision sufficient to cause a real disability.

In regard to hernia, though, such a condition can arise only very rarely, and only under the most distinctive accompanying circumstances which manifest themselves without shadow of doubt. And here is the real crux of the whole problem. Even if the funicular process does persist into adult life, the internal ring is not a gaping opening. Indeed, really, it is not a ring at all, but it is a muscular sphincter closing tightly down on the cord. The fact that, in a particular case, a filament of delicate membrane, thinner than the thinnest tissue paper, also passes down with the cord in no way alters the physical integrity of this muscular ring which fits the structures passing through it as a bottle fits a cork. The normal unstretched ring holds this process constricted to the point of complete impermeability. For this reason, we should speak of a persistent, not a patent, funicular process. Now, for a part of the abdominal contents to be forced through the ring for the first time, tight muscle must be stretched, more probably torn, fascial and aponeurotic structures must be torn, and the force to do this must be enormous. The tearing and stretching must cause immediate, very intense and prolonged pain. There must always be decided shock or collapse. The resumption of work cannot be thought of. The man doesn't need to tell his companions that something has hap-

pened. They can see it and have to carry him away. A physician is demanded post haste. Such a picture, and such a picture only, can accompany the incident when a viscus is driven for the first time through the internal abdominal ring, preformed sac or no sac. Such a case is, of course, compensable. The five criteria of Patterson, plus the sixth, adequate force, must be present in an emphasized and unmistakable degree. For the sake of brevity, such cases will be referred to below as including the six criteria. Yet how different such a case is from the typical cases with which our compensation boards have to deal. A man while at work slips or wrenches himself, feels a pain in the groin, does not stop work, or stops only for a few minutes, tells no one, continues regularly at work the same day and thereafter. Naturally, he feels of himself where he is sore, and, at the moment, or, more often, that evening or several days later, he notices a lump, and with him the question of cause and effect is settled. Very often the process of reasoning is reversed. The employee notices a lump in the groin, recalls some "strain" which occurred not too long ago to be responsible for it, and a dignified compensation board must meet to consider whether this process of reasoning has been correct.

To consider more in detail which cases of claim for hernia should be contested and which should be paid, they may be divided into:

1. Hernias by direct external violence.

2. Hernias of effort, Type 1 (French hernia of force). These are hernias alleged to be due to muscular effort and appearing suddenly and immediately, under adequate and convincing circumstances.

3. Hernias of effort, Type 2 (French hernia of weakness). These are hernias alleged to be due to muscular effort and appearing gradually shortly or remotely after trivial effort, and under inadequate and unconvincing circumstances.

1. *Hernias by Direct Violence.*—These cases, though very rare, do occur. The external force is that caused by a more or less sharp body, like a wagon pole or a bull's horn. The application of the force must be adequate, i. e., all six criteria of the typical compensable hernia must be present, more particularly since such a force must produce considerable subcutaneous laceration of the tissues. For the latter reason, especially if there is considerable edema or subcutaneous hemorrhage, the hernial tumor may not be determined until later. Such cases, rare at best, are rarer still in inguinal hernias. Punctured wounds followed by hernia speak for themselves.

It should be remembered that:

(*a*) Localized blows, however violent to other parts of the abdomen, never yet have produced and never will produce inguinal hernia.

(*b*) A widespread contusion of the abdomen may rarely cause inguinal hernia. The six criteria must be present in unusually marked degree. Rupture of abdominal viscera will almost always be present in addition. A diffuse contusion is more liable to cause diaphragmatic hernia and death than inguinal hernia and a law suit.

2. *Hernias of Effort, Type I.*—These are hernias alleged to be due to muscular effort and appearing suddenly and immediately, under adequate and convincing circumstances. Real cases of this kind will occasionally be met. If a man can reasonably establish that he had no hernia before a certain episode; if this episode was accompanied by a sufficient muscular effort to make possible the stretching and tearing of muscles, fascia and aponeurosis, previously intact; if the immediate results are those that any medical man or intelligent layman who has had the matter explained to him must realize would have to be, that is, if the other five criteria of Patterson are present, then a compensable hernia has been produced. In such a case, the harm can be directly laid to the accident, and, as Coley says, it is immaterial whether a previously empty preformed sac was present or not.

3. *Hernias of Effort, Type II.*—These are alleged to be due to muscular strain and to appear gradually, shortly or remotely after trivial effort and under inadequate and unconvincing circumstances. These persons make the greatest number of claims for compensation, and are responsible for the greatest number of contests before boards and courts. They are, however, exactly those in whom there is always a congenital sac. The hernia has been forming slowly for months or years. The process has been painless; the claimant has been quite unaware that it was going on. The most trivial muscular efforts at work, at play or at home; the ordinary physiologic functions, such as coughing, sneezing, strains at defecation or micturition, have all been helping over a long time, gradually and painlessly, to dilate the internal ring, spread open the persistent process and force intestine or omentum into the congenital sac. The hernia has, in all probability, already been present for sometime before the trivial incident calls the man's attention to his groin.

Even if the incident which the claimant alleges as the sole and final cause of his hernia has made it a little larger and more evident to himself and other laymen, it has not produced any material change and has aggravated nothing in the sense that it has created a new condition which justifies holding the employer responsible for a slightly smaller hernia which has already been present for a long time. The mere fact that a given hernia does, after a certain incident, contain a little more intestine or omentum than it did before does not essentially alter its condition, does not produce a new condition which is more

disabling than it was before, and does not in any way create a new condition for which the employer should be made to pay.

Another possibility is present: We know that the bulging of the preformed sac and the dilatation of the ring have been going on for sometime under the constant minor strains of daily life. The small, persistent, but empty funicular process has finally grown so that now it is an adequate hernial sac. Let us suppose that it was some incident during the course of labor which has finally pushed a piece of intestine into this now open and waiting sac. The last strain is not the cause of the man's having a hernia any more than any other of the countless strains that perhaps ever since birth have gradually been helping to produce the final result. As Moorhead has well said, it is no more logical to hold this final strain to be the cause of a hernia that has been slowly developing for months than it is to consider the last expulsive effort of a woman in labor to be the cause of another human infant's being born. The last labor pain is no more the cause of a baby than a thousand other incidents of the past nine months.

To take a second illustration: A farmer starts to chop down a tree, a crooked weakling, which is not developing properly. After a few blows of the ax, he is called away. A few days later he returns, chops a little, and is again called away; and so on for several times during the next few weeks. Finally, one day he comes, strikes one last blow, and the tree falls. The parallel to what has been happening in this class of hernia is very close—each little strain, causing an additional bulge of the preformed sac, is like each blow of the ax. But the last blow of the ax is not the cause of the tree being chopped down any more than the last effort that finally drives a palpable bit of intestine into a ready and waiting sac is the cause of a hernia. The real reason for chopping down the tree was that it was a crooked weakling. The real cause of the formation of a hernia was the existence of a congenital sac, which had been gradually enlarging through the countless strains of every day life.

A third illustration is more directly apropos. Some one has told of a young foreigner who, to avoid military service, provided himself with a stick which he at frequent intervals placed against his groin and struck with a hammer. After long perseverance, he finally produced double, direct, inguinal hernia. The last blow of the hammer was not the cause of these hernias, any more than was the first, or any of the intermediate ones. Yet, if instead of the last self-inflicted blow he could adduce an accidental blow of a hammer while at work, he would ask, and in many states receive, compensation. In other words, compensation boards would hold that it was the last blow of the hammer which did cause the hernia.

A practical phase of these slowly developing hernias is this: In persons with a persistent funicular process, very often a final complete hernia is necessarily going to occur. A hernia will come anyway, work or no work. If the hernia is actually present at birth, no outsider is expected to pay for it. If it develops during infancy or childhood, no outsider is expected to pay for it. If the final event comes in adult life, why should the employer at that particular time have to pay for it, even if the "final blow" was an incident of work?

Consideration of the Type 2 hernia may be summed up as follows:

1. The six criteria of a true compensable hernia are conspicuously absent.

2. In the vast majority of cases, the actual hernia has already been present and the alleged injury only calls attention to it.

3. If the alleged injury really did first force viscera into the waiting sac, it has simply produced a further stage in a naturally progressing process, and has in no way created a new condition demanding compensation for the final product.

4. Similarly, if an admitted hernia is made larger by a strain at work, it creates no new condition demanding compensation for the final product.

5. Any result, to receive any consideration at all, must be immediately present. If a "sudden" hernia, or an enlargement of an old hernia is noticed, several days after an alleged injury, there is no proof, no evidence and even no probability that the alleged injury had anything to do with it.

V. THE REMEDY

I feel as much as any one that a person with a hernia justly caused by work should be compensated. Also I am just as glad as any one to see assistance given to disabled employees. I believe, however, that the employer should be protected from fraud. He should not be made to pay for an old hernia, and he should not be made to pay for a hernia that was not really caused by work; nor in the gradually developing hernias should he be compelled to purchase the final product because the job happens to be finished while the man is in his employ. In fairness, too, a law that involves a scientific medical question should be determined in accordance with the best scientific medical knowledge on that question. The law should be more clearly and definitely determined. The employer should know which cases he is properly liable for under the law and which cases he can handle as a matter of humane business policy.

The remedy, or at least a great improvement, should not be difficult to obtain. There are two important measures: first, better instruction of the medical profession through the distribution of such literature as

the Report of the Hernia Committee of the American Railway Association; second, an active, systematic and efficient defense of unjust cases. Part of the trouble is that we have let these cases go by the board; it was cheaper to pay than to fight. But the claims are now becoming so numerous that this is no longer the case.

The defense should be made adequate. Competent surgeons of unquestionable standing, outside the company's list, should be obtained to explain the scientific basis of hernia and why the case in question is considered to be an unjust claim.

I think that not many cases will need to be presented in this way before boards and courts will be led to take a much sounder attitude.

VI. COLLATERAL ISSUES

1. *Strangulated Hernia.*—These cases will ordinarily present little difficulty. They will generally be Type I effort hernias, and the degree of force and all six criteria will be unusually prominent. If the circumstances are straightforward, compensation should be allowed. It will, so far as right to compensation goes, make no difference whether or not a definite hernia was known to be present.

Even in these cases, one definite demand must be made, namely, the effort must be distinctly greater than that ordinarily encountered in the course of the particular kind of labor. Otherwise, it should not constitute an accident of labor. It is not sufficient that the strangulation occurs simply during labor. A clerk with a well known large hernia might develop strangulation while sitting, quietly writing. He should not be eligible to compensation. He would be, of course, if the strangulation was caused by moving a heavy desk.

Operation expenses and time lost should be met as provided by the individual law. In my own opinion, disability after any hernia operation should extend for at least three months after date of operation.

Recurrences after operation for strangulation are more common than in simple cases. If recurrence does occur and if it causes disability, it will probably be necessary to accept the later condition as due to the original strangulation.

2. *Operation Elected After Relief from Strangulation.*—There is another point in connection with strangulation which arises occasionally. A case is being contested under my observation now which presents the following circumstances: A man who was known to have a hernia suffered a strangulation under circumstances that were evidently an accident of work. He was taken at once to a hospital and the strangulation was relieved by taxis. The man then, at least after a few days, was as well as ever, and the local condition was the same as it was before.

A brief temporary disability is allowable. However, the man has been so impressed by the gravity of strangulation that after complete recovery he elects to have an operation. Now, it is obvious the man has returned to the condition in which he was before the strangulation. He is perhaps even in just the same condition as when he first began to work for his present employer. It is obviously unfair that the present employer should have to pay for the operation and the subsequent disability, an operation which the man elected himself, but not because the temporary strangulation made it necessary.

A French medical officer reports the case of a cavalryman who, while having great difficulty in sitting a fractious horse and having to pull hard on the lines, suddenly felt a sharp pain in the groin. He at once got off his horse and fell to the ground in great distress. The medical officer was present, reached the man at once, and found a typical strangulated hernia and reduced it at once. The man had never had a hernia before. He continued as a cavalryman for more than two years under the observation of the medical officer and never had a recurrence of the hernia, or any other reminder of the incident. This shows that a temporary strangulation is not necessarily a cause of any disability.

3. Recurrence After Operation for Radical Cure.—The condition of the subject operated on by a competent surgeon may be interpreted in two ways. He may claim, with fairness, that the inguinal canal is as strong as it was before. Indeed, it may be stronger, because a congenital sac has been removed. On the other hand, the scar tissue after the best operations sometimes gradually yields, apparently from no extrinsic reason. With this understanding, recurrent hernias may be divided into three groups:

Group A: (Hernias of Effort, Type I): If a man has remained cured after operation and develops another hernia under conditions which exhibit all six criteria, it should create a compensable condition, just as though no operation had preceded. Furthermore, compensation in such a case should be considered a de novo matter and should be met by the employer at the time. Under these circumstances, it should not be considered as a late result of the previous cause and should not be charged to the employer at the time of the previous accident.

This, however, is an interpretation which should work both ways, i. e., if a man has been well after a radical operation for a hernia originally compensable and suffers a recurrence under aggravated circumstances corresponding to Type I, not connected with work, but in sports, for instance, he should not be allowed to refer the hernia to the compensable accident which preceded the radical operation.

Group B: A man develops a hernia under circumstances justly compensable. He has a radical operation. His case is duly settled, but sometime, even years later, from a trivial cause, or from no apparent cause at all, the hernia recurs. Under these circumstances, the claimant is undoubtedly justly due compensation on account of his new condition. The operation has not really cured him, and he is in just the same situation in regard to compensation as he was before the operation.

Group C: A man has had an operation for a hernia which originally was not connected with industry, definitely obvious since birth, for instance. Such a case should be judged exactly as if he had had no hernia and no operation. If recurrence takes place under typical Type I conditions, he should be compensated. The barrier which broke down might have held up for life had not an adequate force suddenly broken it down. All six criteria, however, must be present, just as when an unoperated canal is broken down for the first time. On the other hand, when an operated canal gives away gradually and under no definite force, it is quite comparable to a Type II hernia and should not be compensated.

VII. THE EXAMINATION TO DETERMINE WHETHER THE HERNIA EXISTED BEFORE THE ALLEGED ACCIDENT

If the claimant is seen within a few hours after the alleged injury, there will generally be little difficulty in deciding whether the hernia was preexistent. As the time increases, the difficulty will increase.

History.—If the claimant admits a previous swelling but "did not know what it was," the situation clears to an extent. The question may still arise as to whether it was aggravated.

A hereditary history will be denied. Berger in 10,000 clinic cases obtained a history of hernia in the antecedents in about 1 in 5. In claim cases, the ratio was 0 in 130. In any event, the question of heredity will have little medicolegal importance.

Searching inquiry should be made as to the possibility of hernia in childhood, and into the previous industrial history. What is the duration of the present work? Has there been a recent change from a sedentary to a laborious occupation? (Compare Turner.)

The history of the alleged injury is most important. The examining surgeon should learn first the nature of the man's usual work and usual muscular effort. He then should determine as exactly as possible the nature of the force. What was the weight? How many were carrying? Did the others let go? Was there a severe effort to maintain equilibrium after a stumble or slip? What was the attitude at the moment of the force? (Strain with the legs apart and the body bent forward is said to be most conducive to the development of hernia.)

Inquiry should next determine the immediate results. What was the character of the pain? Was it immediate? How long did it last? Were there other symptoms, vomiting, collapse, etc.? Was work interrupted and for how long? When was the swelling first noticed? What physical description does the claimant give of it?

The examining surgeon should further be furnished with whatever evidence there may be from bystanders, co-employees, and any physicians that may have seen the claimant before he did.

Thus, it will be seen that the preliminary inquiry should of itself almost determine the judgment. It should develop completely how far the six criteria of a Type I hernia are established.

The Physical Examination.—The claimant should first be examined standing. It should be noted whether the abdominal wall is firmly muscled and well contained. There are three types of lax abdominal wall which strongly indicate a Type II hernia of weakness: first, a bilateral diffuse oval or pear-shaped bulging of the inguinal regions; second, the French abdomen "en bisac" in which there is a transverse constriction at, or just below, the umbilicus, with a general forward and downward bulging of the lower half; third, the "apron" abdomen in which the lower part of the abdomen hangs down in a fold across the anterior pelvic brim and quite hides the inguinal regions from sight from above.

Then with the patient standing, later lying down, a complete examination should be made of the hernia, the canal and the rings. Equally important is a thorough examination of the other usual hernia sites.

Among the conditions which speak definitely against a hernia due to violence or effort are other hernias, known to the patient or not, undescended testis, scars of previous hernia operations, and the forms of lax abdomen noted above.

If seen recently, after the alleged accident, the following additional points prove an old hernia: signs of a truss; lax, flaccid walls, with hernial contents irreducible because of adhesions; hard, thickened, hypertrophied omentum; large external ring, with indefinite, ill-defined edges, especially if it differs markedly in this respect from the other side. The hernia should be small. Scrotal or "large" hernias are very uncommon within a year.

If seen within a few days, the hernia should be small, not larger than a hen's egg, sometimes not reducible. If it has been reduced, it may be impossible for the claimant to reproduce it for examination. A hernia that slips back with no difficulty and reappears with equal ease after a little cough or of itself when the patient assumes the upright position is one that has an old, laxly guarded, well worn path. A ring of the type mentioned in the preceding paragraph is still more significant

here. The ring in a recent, small hernia should differ little from the ring on the other side. If the differences are marked, it has taken time to produce them.

The importance of the external ring in connection with almost any phase of hernia study is considerably exaggerated. I believe that hernia depends entirely on the peritoneum and the structures composing the internal ring and the inguinal canal. I believe the outlet of the canal has little to do with it. I do not believe that a hernial protrusion ever came through an internal ring and canal, to engage an external ring, just because it happened to be large. And on the other hand, if a hernial sac has been pushed through the internal ring and through the inguinal canal, I do not believe that an external ring ever stopped it from going anywhere that it wanted to go. Similarly, I do not believe that of itself a large ring predisposes to a hernia, much less that it should be considered as a hernia of the first degree or a potential hernia.

In a way, I believe that the same thing is true concerning the exaggerated impulse. If no definite mass can be detected and one has to be contented with speaking of various degrees of impulse, it is very doubtful whether a hernia is really there.

VIII. DIFFERENTIATION BETWEEN AN OLD AND NEW HERNIA AT THE TIME OF OPERATION

The operative findings will frequently definitely answer the question in the case of a recent hernia. If several months or a year or more has elapsed since the origin of the hernia, a definite answer after operation may not be so simple. It must be kept in mind that there is a great distinction between the age of the sac and the age of the actual hernia.

The Sac.—One error that is frequently made is to consider that a small, thin, nonadherent, empty sac is necessarily a recent one. The fact is that this kind of sac is the typical persistent funicular process. Its length depends on how far the obliterative process has been effective, but otherwise it may be as thin and delicate as it was at the time of birth. It remains so if not interfered with until old age. It is only the presence of hernial contents which develops thickening, adhesions and the other appearances which we ordinarily associate with an old sac. The same is true in the typical fetal condition in which the covering of the completely descended testis is continuous with the abdominal peritoneum. The smooth, free, delicate structures will remain so from birth to old age. The changes which we ordinarily accept as indicating long standing have begun only when abdominal contents have been forced into these delicate structures and have set up irritation. The longer the delicate type of sac, the more certain it is to be congenital.

If it is adherent to the tunica vaginalis or connected with it by a fibrous band, it is certainly a congenital sac.

In the presence of this type of sac, unless there are other signs, it may be impossible to form any idea as to how long ago it first began to harbor, from time to time, some of the abdominal contents. That is, we can be quite sure that the sac is congenital, but we can form no idea as to how long ago a real hernia began.

No matter whether the sac is a mere dimple at the internal ring or a complete failure of obliteration or anything between the two, there will be no pathologic changes until abdominal contents are driven in and cause irritation. For this reason, I do not think the anatomic relation of the sac to the cord and cremaster gives any indication of the age of the actual hernia. When the sac is thickened and adherent to the surrounding tissues, then we know that the hernia itself is an old one, the age depending in general on the degree of thickening. The white ring due to thickening of the sac at the internal ring is also probably the result of the irritation of hernial contents and is more marked, the older the hernia.

The Contents.—If the contents of the sac at the time of operation show no pathologic changes, they give no indication of the age of the hernia. Adherent intestines and omentum, hypertrophied, chronically congested or inflamed omentum, especially if adherent down to the bottom of the sac, which itself is adherent to the tunica vaginalis, prove hernias of long standing, at least several years.

One need hardly mention that the "sliding hernias," that is, those with cecum or sigmoid mesenteric attachment, and all in the sac, or with the bladder in the sac, are necessarily actual hernias from birth.

Tissues Around the Sac.—In most unusual circumstances, extravasation of blood and other signs of acute trauma will be present, and if so will probably indicate a recent real traumatic hernia.

Strong aponeurotic and muscle structures making up the canals and ring may still be present long after the first appearance of a hernia, especially if it is not large, and if the contents are only occasionally "down."

Weakened atrophied muscles, with large, lax rings, especially with the pillars of the external oblique stretched and poorly identified, are secondary developments due to the long-continued stretching of large hernial contents and always indicate old hernias.

Marked fatty infiltration in the muscle fibers of the conjoined tendon always indicates an old hernia.

PATHOGENIC PTOSIS OF THE RIGHT COLON*

E. P. QUAIN, M.D.

BISMARCK, N. D.

The intestinal mesentery undergoes a torsion in early fetal life, during which the right colon, that is, the cecum, ascending colon and nearly half of the transverse colon travel from left to right across the duodenum and toward the right kidney. According to most of our textbooks, the normal location for the hepatic flexure is in front of the right kidney and near the right border of the liver. It is a fact, however, revealed by fluoroscopic examinations and by surgical inspections, that the hepatic flexure in many persons has failed to rotate sufficiently far to the right to become fixed by the phrenocolic ligament in the classic situation just mentioned.

For the purpose of determining the position of the hepatic flexure in healthy persons, a series of fluoroscopic examinations with barium meal were carried out by my associate, Dr. V. J. LaRose, on twenty-five undergraduate nurses, all with normal gastro-intestinal function. The interesting findings were that more than half of them had an abnormally low right colon. In two of these young women who had never suffered from constipation or other abdominal symptoms, the hepatic flexure was very near the anterior superior spine of the ilium, and the cecum rested in the pelvis.

While many persons may go through life without serious consequences resulting from an abnormal descensus of the right colon, others are not so fortunate. Given a person with a certain degree of congenital coloptosis which does not cause any marked disturbance during childhood, and impose on this person, during early manhood or womanhood, the hard stress of physical toil, without sufficient rest, irregular dietetic and physiologic habits, poor health from any cause, repeated child-bearing (for the majority of the patients are women), and symptoms and complications are very likely to attend the ptosis.

In order that the fetal colon may rotate in a semicircle about the upper abdomen, it is necessary for it to have a fairly long mesentery. If the embryonic mesocolon fails to reach the right border of the liver, or if by some premature agglutinating process it is hampered in its rotation, then the hepatic flexure and the entire right colon assume an

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* Read before the South Dakota State Medical Association, Huron, S. D., May 18, 1922.

* The terms "colorrhaphy," "colofixation," "cecofixation," "cecopsoas" and "colopsoas," as used in this article, were employed freely by Duval (Footnote 3).

abnormally low position. When this takes place, the cecum and ascending colon retain their mesentery, and, instead of becoming agglutinated to the muscles of the back, they are permitted to hang more or less loosely on this mesentery. In many persons, it is found that the agglutination and fixation of the hepatic flexure have taken place almost normally, while the cecum and ascending colon are still freely movable on their mesentery. When there has been complete failure of hepatic flexure fixation, the entire right colon hangs from a continuation of the iliac mesentery, extending upward and fusing with that of the transverse colon, and the weight or downward pull of the entire right colon is exerted from the root of this mesentery, which is attached in close relation to the duodenum, pancreas, bile ducts and solar plexus.

It would seem that whenever Nature neglects to follow out her usual plan of fixing the colon to the right flank in early embryonic life, she makes an attempt to repair her shortcomings by introducing certain ligamentous bands to prevent or at least to limit the hypermobility. It is hard to find any better explanation for the appearance of the pericolic bands and membranes. Their development at the places and in the directions where they are aiding most effectually to affix an abnormally movable segment of the colon seems to have something purposeful in it. The evolutionary reason for these abnormal structures, as stated by Lane,[1] Coffey,[2] and others, is to me quite evident. Unfortunately, this delayed attempt at fixation is not effective, and moreover it very often leads to interference with function and the production of symptoms of various kinds and severity.

The pericolic bands or membranes of most importance in the study of coloptosis are: (1) a modified phrenocolic ligament which attaches the hepatic flexure to the undersurface of the liver, to the posterior peritoneum, to the kidney capsule, or to the peritoneum of the right flank; (2) a membrane from the lateral abdominal wall extending obliquely down over the ascending colon, the so-called Jackson's membrane. Its purpose is evidently to lift and fix the ascending colon and cecum when these are abnormally mobile on their mesentery. Severing this membrane causes an increased mobility and descent of the cecum. Colopexy causes it to relax. Neither of these membranes is present in those who are born with a normally fixed right colon. (3) A membrane, often multiple, running from the right half of the transverse colon and its mesentery upward, to become attached to the second portion of the duodenum, gallbladder, gastrohepatic ligament, or under-

1. Lane, W. A.: The Operative Treatment of Chronic Intestinal Stasis, New York, Oxford University Press, 1918.

2. Coffey, R. C.: Phila. M. J. **10**: Oct. 11, 1902.

surface of the liver. In cases of midline or general visceroptosis, this supporting band is often reinforced by a second membrane formation which holds the duodenum toward the liver.

TYPES AND DEGREES OF THE LESION

For the successful management of a given case of coloptosis, it is necessary that we have a clear understanding not only of the congenital origin, the progress and the complications, but also of the various types and degrees of the lesion. The classification given by Duval [3] in his discussion of the anatomic pathology of fecal stasis in the right colon is in harmony with my own observations. He gives the following general types:

1. *Simple Mobile Cecocolon.*—In this condition only the cecum and the lower segments of the ascending colon are hypermobile on a mesentery. The hepatic flexure is fixed in the normal, or nearly normal, position on the posterior abdominal wall. A pericolic membrane, varying in size, is present on the ascending colon in practically every case. The cecum is thin, distended with gas, and always contains more or less stagnant liquid feces. The symptoms resemble those of our classic conception of "chronic appendicitis."

2. *Complete Right Coloptosis.*—In this condition the whole right colon hangs by a mesentery, and without direct attachment to the posterior abdominal wall. Pericolic membranes are much in evidence, but they neither fix the bowel to the back nor prevent the hypermobility. If the membranes are severed, the entire mesentery comes plainly into view. Symptoms are referred toward the epigastrium and are easily mistaken for evidence of duodenal or biliary disease. The right kidney may have become prolapsed, attached to, and closely follow, the hepatic flexure.

3. *Infection of Colonic Wall.*—Several degrees of colitis, mucous and parietal, as well as pericolitis, are recognized. Duval subdivides the condition into three different types. In mucous colitis, there is an edema of the mucous membrane with areas of ecchymosis and necrosis. The lymphatic glands are large and soft. In parietal colitis, the whole bowel wall is thickened. Lymphatic involvement is evident throughout the retroperitoneal space. Inflammatory adhesions appear, which in course of time cover the whole segment involved. They restrict, retract, and fix the previously hypermobile colon. The adhesions may involve the omentum, transverse colon, and other neighboring organs in the upper abdomen or pelvis. From the old retracting adhesions, as well

3. Duval, P., and Roux, J. C.: Arch. d. mal. de l'app. digestif. **10**:705, 1919-1920.

as from the absorbed products of infection, secondary disease may follow, in the gallbladder, stomach, duodenum, pancreas or kidney. Stenosis and obstruction in the colon itself frequently result from the network of fibers. Constipation is intensified and alternates with diarrhea of cecal origin. During this stage, a secondary anemia is present, with a decrease of polymorphonuclear cells and an increase in lymphocytes. The skin becomes darker than in mild hemolytic jaundice. The patient's general health, both physical and mental, is

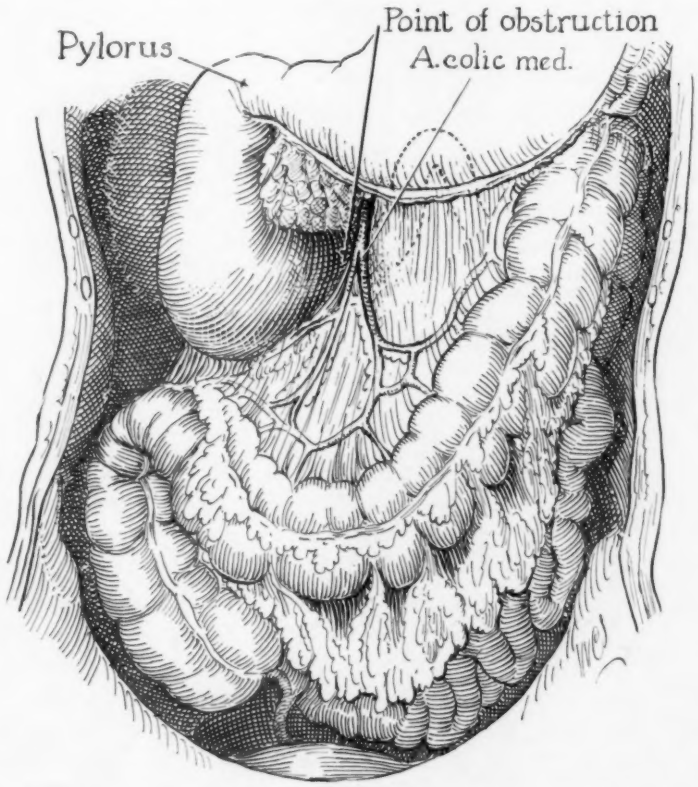

Fig. 1.—Right coloptosis causing obstruction of the second portion of the duodenum (from Duval).

definitely below par. An intermittent elevation of temperature is present, during which time *B. coli* may be found both in the urine and in the blood.

Many conditions in a patient's life help to increase the congenital hypermobility and abnormal descent of the colon. The most active factors are the following: occupations which require standing upright during a large part of the working hours; any intervening illness which causes disappearance of fat from the body in general and

from the mesentery and retroperitoneal space in particular; frequently repeated child-bearing, by attenuating and weakening the anterior abdominal muscles, thereby giving more room for descent into the lower abdomen; insufficient food; physical and mental strains, in short, every condition which tends to cause deterioration of the normal tone and human well-being.

SYMPTOMS

Most of the symptoms induced by coloptosis are due to the dragging of the mesentery or pericolic membranes and to the constant fecal stasis. The symptoms are many and diverse, but may be grouped into three general classes: pain, constipation and intoxication.

The pain is of two types, that produced in the immediate vicinity of the colon, and that produced by dragging on other organs. The former is a chronic discomfort or pain in the right side of the abdomen, often present from childhood. It may be constant, or may be periodic. It is aggravated by occupations requiring much standing, heavy work, and foods which cause fermentation and intestinal distention. It is relieved by rest, especially when lying on the right side. It disappears temporarily after a thorough evacuation of the colon. This local pain often comes on acutely, in attacks, and may be associated with emesis and some rigidity of the abdominal wall. But the attack is never very severe, and it passes away gradually in a day or so. There is rarely any elevation of temperature, and leukocytosis is absent. A diagnosis of appendicitis is usually made, and the appendix is not infrequently removed either in one of the acute attacks, or, more frequently, on a supposition that chronic appendicitis causes the pain. Appendectomy relieves the symptoms by the enforcement of a week or two of absolute rest, and by the dietetic and occupational care which is taken for a time following the operation; but after the patient resumes his usual mode of living, the old symptoms recur in most cases.

Pain is produced at a distance, by the dragging on the mesentery. In those instances in which the mesentery at the hepatic flexure has become more or less attached to the right kidney, but is otherwise free, the kidney is liable to become dislodged and displaced downward with the colon. Pain and other symptoms due to the kidney ptosis are then invoked.

When the entire right colon is free and hanging by its mesentery, traction is exerted across the second and third portions of the duodenum. The pulling effect is emphasized by the firmly fixed position of the middle colic artery running within the mesentery, and by the supracolic membranes which have been mentioned. The variety of symptoms that may be produced in the gallbladder, duodenum and stomach is enough to cause serious confusion in the diagnosis of cholecystitis and

duodenal or gastric ulcer. The success of treatment, medical or surgical, directed to these organs will depend in no small measure on the recognition and management of this pathologic factor.

The pericolic membranes are very important agents in causing pain, as well as other symptoms. The membrane producing pain most fre-

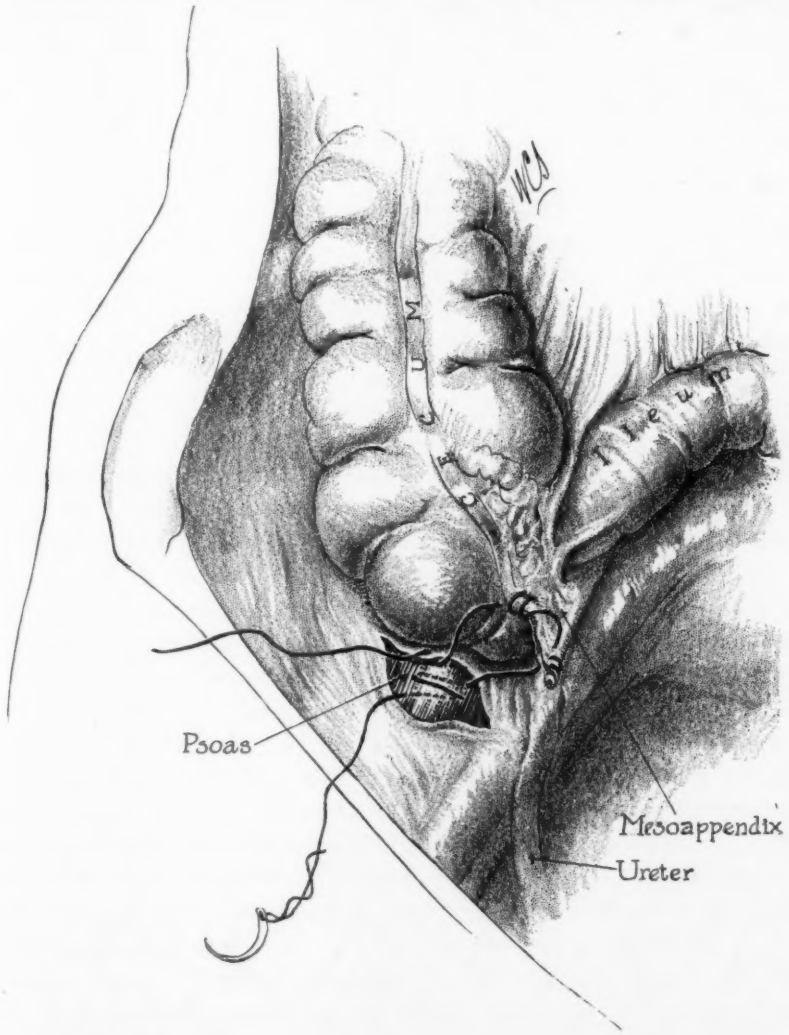

Fig. 2.—Method of fixation of hypermobile cecum after appendectomy.

quently is, perhaps, the one located on the outer surface of the ascending colon. I have found it only in the presence of a mesocolon. When this membrane is attached to the parietal peritoneum over a very small area, it is capable of causing quite acute pain. After colofixation, which takes the tension off the membrane, the pain disappears.

The smaller the sensitive peritoneal area involved in a membrane or adhesion, the more severe the the pain. Wide and extensive adhesions cause less discomfort because the dragging effect is distributed over many, instead of a few, nerve endings.

Constipation is an early and perisistent symptom of coloptosis. It should be differentiated into two types, that due to a retardation in the left colon and that due to stasis in the right. The former does not, as a rule, cause very serious consequences. The drying fecal masses contain almost no living bacteria or toxins, and many persons live in good health with very infrequent evacuations. Constipation due to delay in the right colon is much more harmful. Cecal contents are always liquid, and contain innumerable bacteria, some of which are pathogenic. Incompletely digested and absorbed food products are always present in the cecum to feed the bacteria and to produce a continuous supply of toxins. In the course of time, the cecal wall becomes more and more distended and atonic and never evacuates except from overflow. The mucous membrane loses its protecting function, and toxins and even bacteria enter and find their way to the lymphatics and thence to the general circulation. An albuminous exudate demonstrated in the feces indicates a serious degeneration of the mucous membrane. Some patients are liable to have spells of diarrhea alternating with constipation, which means that the left colon is sensitive to the irritating overflow from the right. In others the left colon may have learned to absorb the water from the overflow and to exercise regular defecation, thus helping to conceal the functional changes of the right.

Intoxication, or absorption of pathogenic products from the fallen, paralytic and helpless cecum, causes a lymphangitis and lymphadenitis in the mesocolon. The enlarged lymph glands are clustered along the blood vessels. Even lymph nodes in more distant regions, near the aorta, may be affected. The local infection travels through the bowel wall, and then the peritoneum reacts by establishing a new set of membranes, inflammatory adhesions. The effect of these adhesions, often in combination with the evolutionary membranes, is to produce various degrees of obstruction to the passage of the intestinal contents. Absorption of toxins lays a foundation for a long list of constitutional symptoms, including dizziness, headaches, nausea, malaise, asthenia, mental depression, and in some instances chronic mental disease.

It is possible to form a fairly true estimate as to the location of the cecum and hepatic flexure by inspection, palpation and percussion. In patients with thin abdominal walls, the fingers can easily make out a cecum mobile in its changing situations, depending on the posture of the body. However, no semblance of guesswork needs to be entertained

in making a diagnosis, since the roentgen ray enables one to visualize exactly the conditions. By means of fluoroscopic examination, we can determine the position of the colon as well as the other parts of the gastro-intestinal tract; the presence and location of stasis, dilatations and obstructions, and the degree of mobility of the organs. I shall not attempt to discuss the various forms of roentgen-ray technic required to obtain the fullest amount of information.

TREATMENT

The success of treatment for well marked coloptosis will be proportionate to the intelligence and cooperation rendered by the patient. In the medical treatment of the disease, it is almost impossible to obtain any satisfactory results in those who are too ignorant to grasp the meaning of the various requirements. In the care of the surgical patients, it is necessary that instructions be followed understandingly for a certain length of time after operation, depending on the patient's age. The younger the patient subjected to colofixation, the more certain and rapid is the cure.

It is, therefore, best that all patients at first be given a course of medical treatment, partly because some of the milder cases will be much improved, and partly because all the patients need to learn in detail how to manage their own conditions, or to keep up postoperative treatment. For best results, it is required that the patient go to bed in a hospital for two or more weeks. The patient is placed in the Trendelenburg position, on an incline of at least 30 degrees. This is maintained with intervals of rest for several hours each day. It is kept up for an hour after each meal. So far as possible, the patient should not raise his shoulders from the bed at any time. An enema is given at least once a day, and on the bedpan. Meats and albuminous foods are avoided. The diet is made up chiefly of vegetables, carbohydrates and fruits. This is to retard the putrefactive bacteria and to aid the fermentative flora in the cecum. Lactose in liberal amounts is of definite value for this purpose, since it passes almost unchanged through the small intestine.

The Trendelenburg posture gives the patient several distinct benefits. All the viscera, including the ptotic colon, sink toward the epigastrium, making a movement opposite to that which produced the symptoms. The right colon empties itself more easily. Visceral circulation is restored to areas which have been indifferently supplied with blood when the patient is in the erect posture. The dragging on the duodenum, stomach and bile ducts is relieved. The pulling and irritation on the solar plexus and sympathetic nervous system are removed. The relief from sympathetic nerve irritation is a circumstance which I believe to

be of very great importance. It is my belief that this is a greater factor in producing neurasthenia in those who have visceroptosis than is the absorption of intestinal toxins.

It is interesting to watch the favorable progress in a patient who has suffered definite symptoms from coloptosis after from two to four weeks of this treatment. The abdominal pain and distress are relieved or gone. Bowel movements are obtained more easily. The nervous and mental tension has given place to a feeling of rest and well-being. Symptoms of toxemia have disappeared. The appetite is improved; the blood findings approach normal, and the body weight increases several pounds.

The next problem is to prevent the colon from resuming its original malposition when the patient is allowed to leave the bed For this purpose, a binder or corset, with a pad, is so adjusted that the lower abdominal cavity will become reduced in size and thus have less space into which to invite the ptotic organs by gravity. That a pad properly made and applied can do this effectively is proved by many patients who have learned that they become uncomfortable whenever they try to go without it. On leaving the hospital, the patients are instructed to lie down in the Trendelenburg posture for at least twenty minutes after each meal. This posture must be used after retiring and before applying the pad each time. They are also taught how to make use of the knee-chest posture if the other, more cumbersome, position is impracticable at any time. This position may also be used after going to bed at night and while putting on the pad and binder.

While many patients learn to carry on their daily work in comfort by the method described, the majority are improved only temporarily while under medical regimen. For more lasting relief, it is necessary to resort to surgery. By keeping in mind the gradations of pathologic anatomy, the indications for the various types of operation become fairly well defined. When the colonic wall has become infected and thickened and pronounced lymphadenitis and multiple adhesions are present, no operation short of right colectomy will cure the patient. Right colectomy should not be considered too formidable a procedure for these patients, in view of what it has to offer. With proper technic, the operative risk is very small.

In the presence of cecum mobile of mild degree, a fixation of the caput coli to the root of the meso-appendix should always be performed after appendectomy. It is my conviction that this fixation of the cecum, incidental, accidental, or intentional, has much more to do with the relief from symptoms after operation for so-called chronic appendicitis than the removal of the appendix itself. It is also my firm conviction that if a cecum mobile is present and not fixed when the appendix is

removed for so-called chronic appendicitis, the symptoms of chronic appendicitis will recur within a few weeks after the operation.

When the cecum and ascending colon are both ptotic and hypermobile on a mesentery, a more radical fixation to the psoas muscle is made. An incision is made through the posterior peritoneum, opposite

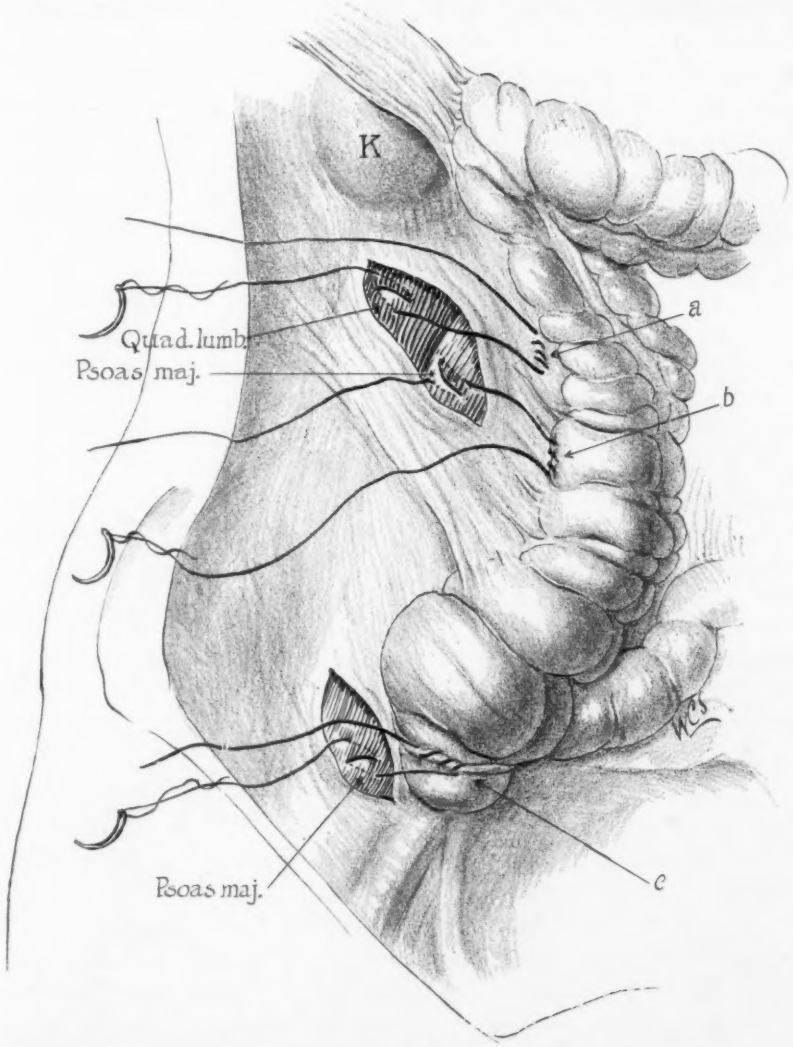

Fig. 3.—Methods of colofixation: cecum to psoas minor, colon to psoas major and colon to quadratus.

the normal location for the cecum, and the cecum is sutured to the muscle with two or three sutures of chromic catgut. When a psoas minor muscle is present, which is the case in about one half of the patients, then the sutures should include it.

When most of the ascending colon is free and involved in the hypermobility, a second peritoneal incision is made somewhat higher, over the edge of the psoas, and two other chromic catgut sutures are introduced. A very solid fixation is obtained by placing the sutures into the posterior longitudinal line of the colon, but this is likely to cause considerable backache in the first few weeks after operation and may involve a risk of too firm a fixation in some cases. All that is necessary is to pass the needle through the subperitoneal tissues at the margin of the mesocolon. It will do no harm if some of the smaller blood vessels to the colon are included in the suture. They add firmness to the fixation. It need not be stated that care must be exercised in order to avoid damaging the larger arterioles. The bowel mucosa must not be pricked with the needle, or infection is certain to follow the operation.

When there is a complete right coloptosis, a still higher fixation should be made at a point representing the hepatic flexure. It is not possible to do this to the back muscles because the kidney, with its blood vessels, and the ureter are in the way. My practice is to open the posterior peritoneum and pass two or three sutures through the areolar tissue in front of the kidney. If there is only a small amount of fat present, the muscles near the twelfth rib are easily reached at this point. If there is an abundance of fat, it has seemed best not to pass these sutures deeply under the peritoneum but to be satisfied with a broad peritoneal attachment under the liver.

When the right kidney is definitely prolapsed with the colon, the fatty capsule is split over the dorsum and peeled loose from the kidney. The tuft of fat thus freed externally, but attached in front of the kidney pelvis, is gathered together with two or three sutures of chromic catgut and sutured firmly to the quadratus lumborum. This forms a shelf on which the kidney rests, and is a much better procedure than all attempts to anchor the kidney itself. The shelf blocks the way for all future chances of recurrence of the kidney ptosis. When this technic for kidney fixation is called for, the colon is sutured into the newly made kidney shelf. A rubber cigaret drain provides an outlet for the inevitable oozing which will follow the kidney operation.

Approaches to the fields of operation are obtained either through a double split-muscle incision or through a transverse opening of the abdominal wall. I [4] have previously described the principles and technic of these incisions.

After the adoption of the technic of colofixation, as described above, the results obtained from the surgical treatment of coloptosis have been very satisfactory in my experience. Since my attention was

4. Quain, E. P.: Abdominal Incisions, Arch. Surg. **1**:585 (Nov.) 1920.

first attracted to visceroptosis, about twelve years ago, several methods of surgical treatment for coloptosis have been tried out.

Suspension of the transverse colon to the anterior abdominal wall, as recommended by Rovsing,[5] Coffey, and others, did not prove satisfactory for the treatment of this type of ptosis, although the method undoubtedly is of distinct service in certain midline ptoses of an

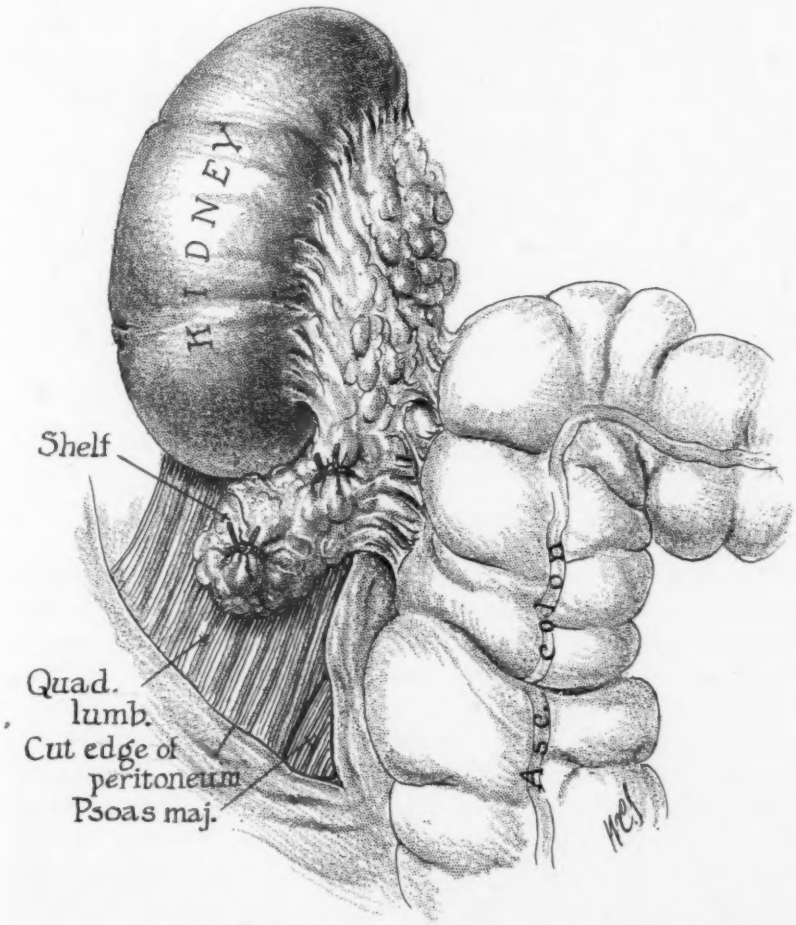

Fig. 4.—Kidney shelf made from fatty capsule.

acquired nature. In some patients, new symptoms developed after operation, such as epigastric pain and interference with gastric and colonic functions. Moreover, it gave no relief to a ptotic cecum. Various types of colorrhaphy and peritoneal "pexies" were also employed. From these the best results were obtained by shortening the longitudinal

5. Rovsing, T.: Ann. Surg. **57**:1 (Jan.) 1913.

bands of the ascending colon, provided the sutures were so placed that the weight of the cecum was transferred from a pain-producing pericolic membrane to the ascending colon above the membrane. Suturing of the cecum or its mesentery to the posterior peritoneum externally to the colon, while both pain and constipation might be temporarily relieved, was almost invariably followed by recurrence of cecoptosis and symptoms. I have operated on a number of patients after previous colorrhaphies, and from the findings at operation it was evident that a ptotic colon will in the course of time overcome and undo any attempt at fixation which is based on peritoneoperitoneal adhesions.

Eleven colectomies, eight of the right colon, and three total excisions, have been made because of colitis due to ptosis and stasis. The only patient who died after operation for coloptosis was one in whom a septic retroperitoneal infection began a few days after operation, a right colectomy. This was a tragic lesson teaching the danger of opening lymphatics behind an infected colon without proper provision for drainage. One patient who suffered from melancholia before the operation was not improved mentally, although the abdominal symptoms were evidently much improved. One patient suffered a severe attack of influenza and bronchopneumonia immediately after operation and was treated for fecal fistula and bronchial infection for three months. The patient was then discharged cured. The remaining eight are practically well.

The technic of incision through the posterior peritoneum and fixation directly to the muscles of the back has, up to date, been employed on more than seventy patients. Personal reexaminations and answers to letters of inquiry have given postoperative information from fifty-two of those who were operated on three months ago or more. It should be stated that the syndromes of these varied in severity from those that we formerly associated with chronic appendicitis and constipation to more aggravated forms of renal, biliary, and duodenal complications. Cecopsoas or colopsoas fixation for simple mobile cecocolon was made in thirty-six of the fifty-two patients. Fixation of the entire right colon was accomplished in the other sixteen. Because of complications from coloptosis, nine nephropexies, five duodenojejunostomies, and four cholecystectomies were performed, in conjunction with colofixation. Eleven patients had submitted to previous unsuccessful operation, or operations, for the cure of chronic appendicitis, cholecystitis, and duodenal ulcer.

The following is a brief summary of the results following colofixation: Twenty-two, or 61 per cent., of the thirty-six who had cecopsoas and colopsoas fixation are free from all previous symptoms, and twelve, or 75 per cent., of the sixteen with complete colofixation are

symptom-free. The majority of the remainder, about one third of the total number, named constipation as the symptom which had not been entirely overcome by the operation. Four complained of occasional backache, and three had some colicky abdominal pains. More or less relief from previous symptoms was acknowledged by all but three, who stated frankly that they had received no benefit from the operation. Not the least satisfactory were the results in those patients who were relieved of symptoms in other organs, the kidney, gallbladder, and duodenum, and in whom the most radical and multiple interventions were undertaken.

It will be noted that the lowest percentage of cures was found after the more simple surgical procedures. It was natural that the surgeon, traveling on a poorly blazed surgical path, in the beginning of this method of treatment, should hesitate before employing the more radical technic, and the result was that many patients did not receive surgical treatment in proportion to the degree of the lesion. In the light of more experience, I know that failure to excise an infected or paralyzed colonic segment has been the cause of persisting constipation and other symptoms in several patients. It is improbable that a chronically overdistended and atonic cecum can regain its tone and function from any change in its position. Microscopic sections made from the stretched out longitudinal bands of such a cecum show degeneration of muscle fibers, even in the absence of gross evidence of bowel wall infection.

It must be admitted that sufficient time has not elapsed to permit one to make any assertion as to the permanency of cure following colofixation by the method described. However, a number of patients, formerly chronically ill, who have been free from previous symptoms and capable of a full enjoyment of work and play during more than two years following the operation have given an assurance which amply justifies confidence for the future and a continued application of the treatment.

CONCLUSIONS

1. Coloptosis is a very common anatomic abnormality.

2. Comparatively few of those who have a ptotic colon suffer serious symptoms as a consequence, but the incidence is, nevertheless, much greater than we formerly supposed.

3. Some of the effects of coloptosis are translated to other abdominal organs which may then give rise to a new set of symptoms, thus obscuring the original and chief cause of the trouble.

4. Medical treatment gives relief in most cases and should be given a thorough trial in all cases, but its ability to cure is doubtful in any case.

5. Surgical treatment is as successful in these lesions as in many other so-called surgical diseases and promises better results as experience accumulates.

6. Chronic appendicitis is an infrequent disease, and the term should be restricted to those comparatively few instances in which there actually is a chronic lesion of the appendix.

CARCINOMA OF THE APPENDIX *

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Although carcinoma of the appendix is no longer considered a rare disease, the condition may easily be overlooked unless a careful routine examination is made of all appendixes removed. The surgeon often sees an obliterated, or partially obliterated, rather harmless appearing appendix, and he is in doubt as to the advisability of its removal. It has been shown that one in every fifty-three of such appendixes is carcinomatous.

In 1911, MacCarty and McGrath [1] reported from the Mayo Clinic the results of the study of 5,000 appendixes and demonstrated that one of every 225 was carcinomatous. In a later series, they found eighteen (0.6 per cent.) of 3,039 specimens to be carcinomatous.

With a view to determining the prognosis, the forty cases reported by MacCarty and McGrath have been followed, also twenty-four [2] later cases in which specimens had been studied microscopically.

In ninety cases of primary carcinoma of the appendix collected from the literature by McWilliams [3] in 1908, seven patients were alive and well after five years, thirteen after three years, and twenty-one after two years. Kelly [4] reported a case in which the patient had been in poor health for nine years. He had had constant sharp pain in the right iliac fossa and tenderness in the incision. In 1915, Meyer [5] reviewed the literature to date, compiling the reports of 269 cases,

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* This study was made in the Section on Surgical Pathology under the supervision of Dr. William C. MacCarty.

1. MacCarty, W. C., and McGrath, B. F.: Clinical and Pathological Significance of Obliteration, Carcinoma, and Diverticulum of the Appendix, Surg., Gynec. & Obst. **12**:211-220, 1911.

2. MacCarty, W. C., and McGrath, B. F.: The Frequency of Carcinoma of the Appendix, Ann. Surg. **59**:675-678, 1914.

3. McWilliams, C. A.: Primary Carcinoma of the Vermiform Appendix: A Study of Ninety Cases, Three Previously Unpublished, Am. J. M. Sc., **135**: 822-850, 1908.

4. Kelly, A. O. J.: Primary Carcinoma and Endothelioma of the Vermiform Appendix, Am. J. M. Sc. **135**:851-856, 1908.

5. Meyer, L. B.: Primary Carcinoma of the Appendix: A Review of the Literature, with a Report of Three Additional Cases, Surg., Gynec. & Obst. **21**: 354-360, 1915.

including three of his own. Since then I have found reports of twenty-four cases including twelve by Reimann.[6] These, with the twenty-four here reported, bring the total to 317 cases.

PROGNOSIS

Thirty-seven of the sixty-four patients observed in the clinic were traced. Two had died from accident or of conditions in no way related to the disease and two had died of postoperative complications. The remaining thirty-three are living and, in most instances, well (Table 1).

Operation resulted in cure of the malignant condition in 100 per cent. of the patients traced. Carcinoma of the appendix, then, assures the most favorable prognosis of all forms of malignancy of the gastro-intestinal tract as indicated by this percentage of cures. It is significant, however, that the surgeons had not made a positive diagnosis of malignancy in any cases in the first two series reported by MacCarty

TABLE 1.—PROGNOSIS IN THIRTY-THREE CASES OF CARCINOMA OF THE APPENDIX

Cases	Years Since Operation	Cases	Years Since Operation
1	16	1	7
1	15	2	6
1	13	1	5
5	12	2	4
4	10	3	3
3	9	3	2
3	8	3	1

and McGrath. In only five of the twenty-four cases here reported was a positive surgical diagnosis of carcinoma made, although the lesion was suspected in four other cases.

Although this report is confined to cases of primary carcinoma of the appendix, a number of cases were reviewed in which carcinoma was present in both the appendix and cecum, suggesting a relationship between the two. Pathologists disagree on the possibility of carcinoma of the large bowel originating in the appendix; but until the point is more definitely settled, such a possibility must be considered.

CLINICAL SIGNS

There is little of significance in the clinical history of these cases. Sixteen of the twenty-four patients observed since 1911 were females; eight were males. The average age of the women was 42 years, of the

6. Reimann, S. P.: Primary Carcinoma of the Vermiform Appendix, Am. J. M. Sc. **156**:190-201 (Aug.) 1918.

men 40. Twelve gave a history of previous trouble in the appendix; twelve gave histories of other symptoms. The average duration of symptoms of appendicitis was six and eight-tenths years.

The facts of value in these data are that 50 per cent. of the patients gave a history of previous trouble and that the disease is seen twice as often in women as in men. These findings are in accord with those of other observers.

McWilliams reported that 83 per cent. of seventy-six patients gave a history of previous trouble in the appendix. In forty-seven of seventy-eight cases, the condition was present before the age of 30. He remarked that in 60 per cent. of the cases, malignancy before the

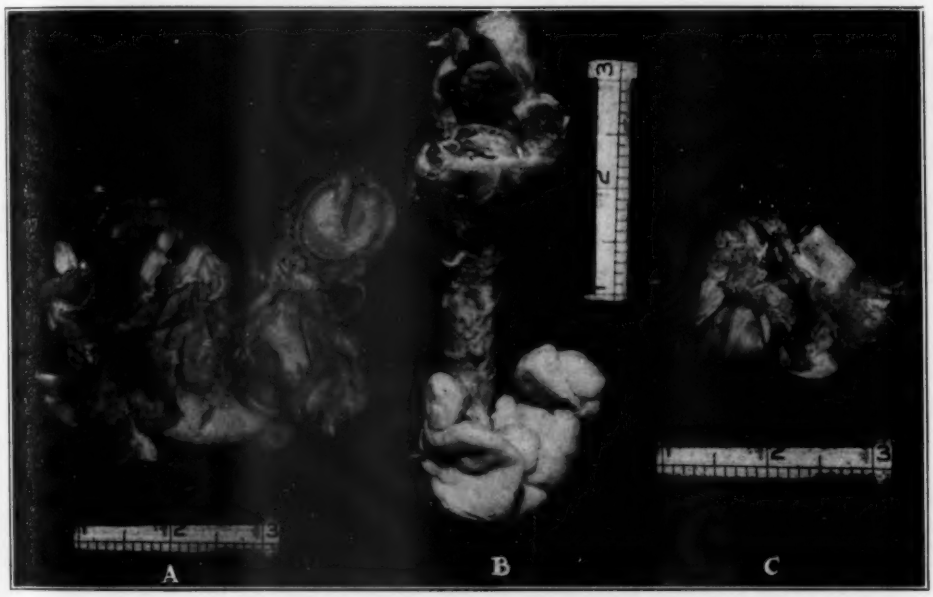

Fig. 1.—*A*, cross-section of obliterated tip of appendix showing carcinoma; *B*, extensive involvement of the base of the appendix by carcinoma; *C*, specimen of a colloid carcinoma involving the tip of the appendix

age of 30 is in marked contrast to the age incidence in malignant tumors of the remainder of the intestinal tract. Rolleston [7] reported 180 cases of carcinoma of the intestinal tract, exclusive of the appendix, with an average age of 49 years; these patients were twenty years older than the patients with carcinoma of the appendix.

Deaver, in an analysis of 3,000 cases of simple appendicitis, showed that 69 per cent. occurred in patients before the age of 30,

7. Rolleston, H. D., and Jones, L.: Primary Malignant Disease of the Vermiform Appendix, Tr. Med.Chir. **89**:125-153, 1906.

and that 38 per cent. of the patients were females and 62 per cent. males. No explanation has been offered for the complete reversal in frequency of the two conditions in the two sexes.

A history of previous trouble in the appendix in 50 per cent. of the Mayo Clinic series is in accord with the pathologic findings; the lumen is usually found obliterated, indicating a previous inflammatory lesion. This is an important surgical point, and shows that in every case with a history of trouble in the appendix this process should, if possible, be examined carefully for signs of malignancy. Since surgeons have learned to recognize this condition more readily, they have been more careful to remove all appendixes in which there is a suggestion of malignancy. One result has been the discovery of many malignant appendixes that might otherwise have remained undisturbed.

TYPES OF TUMORS

Considerable doubt exists concerning the pathology of these tumors. Mallory[8] says: "It is difficult to decide the exact nature of certain small tumor-like collections of epithelial cells occurring occasionally in the appendix, but also more rarely in the small intestine. They resemble a carcinoma in structure and are found most often in young persons. The cells are small, are grouped in solid masses, and may occur not only in the mucosa but also in the muscle coats and subserosa. In the appendix they often look as if they had started from the mucosa and more or less completely destroyed it, and then infiltrated the surrounding muscle and fibrous tissue. On the other hand, they show little or no activity of growth and there is no evidence of reaction on the part of the tissue around them. They are regarded by some as a local tissue abnormality comparable to the congenital nevi of the skin."

In 59 per cent. of seventy-one cases reviewed by McWilliams, the carcinoma occurred at, or near, the tip, and in 33 per cent. no tumor was visible to the naked eye. In twenty-three of forty-two cases, or 55 per cent., one or more solid tumors were visible.

In the Mayo Clinic series of twenty-four cases, the carcinoma was located at the tip in twenty-one, at the base in two, and at the middle in one.

The tumor in situ grossly resembles concretions within the lumen. On transverse section the lumen is seen to be obliterated by a solid growth which is homogeneous and fibrous in appearance and presents an orange color in specimens preserved in liquor formaldehydi.

Certain observers, such as Neugebauer, have classified the majority of tumors of the appendix as endotheliomas, partly on account of the type of cell, and partly on account of the benign nature of the tumor.

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8. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914, p. 389.

Fig. 2.—Alveolar arrangement of the cells in carcinoma of the appendix.

Fig. 3.—Involvement of the submucosa and the musculature by carcinoma.

Graham in a review of 172 cases reported in the literature up to 1908 divided carcinoma of the appendix into two main groups, the spheroidal cell and adenocarcinoma. The spheroidal cell carcinoma has been described as scirrhous, medullary, simple, alveolar and basal; but the detailed descriptions indicate that the cases recorded under various names are practically identical. This type occurs in 73.8 per cent. of cases. The second type, adenocarcinoma, includes cases described as cylindric-cell carcinoma and colloid adenocarcinoma. This type includes 18 per cent. Five and eight-tenths per cent. of the cases not included in either group are recorded as transitional, between spheroidal-cell and adenocarcinoma; 2.3 per cent. of the cases are called colloid carcinoma. The average age in cases of adenocarcinoma and of colloid carcinoma is somewhat greater than that in cases of spheroidal carcinoma; it corresponds more closely to the age at which carcinoma of similar type occurs in the large intestine.

There is a further difference between the two types in the degree of malignancy, as was pointed out by Rolleston and Jones. In only one

TABLE 2.—AVERAGE AGE IN CASES OF VARIOUS TYPES OF TUMOR

Type	Cases	Average Age
Spheroidal	127	27.2
Adenocarcinoma	31	39.5
Transitional	10	29.8
Colloid	4	44.7

case of the spheroidal-cell type, in which the growth was undoubtedly primary in the appendix, was there invasion of the cecum or spread by metastasis. In six of thirty-five patients with adenocarcinoma or colloid carcinoma, however, carcinoma spread to the cecum or to the abdominal glands by metastasis. The average age in these patients was 51.8 years. Recognition of the difference in the degree of malignancy of the two types is important, since the prognosis must be guarded when adenocarcinoma or colloid carcinoma occurs, especially in middle-aged patients.[9]

The microscopic examination reveals irregular masses of epithelial cells closely packed in alveoli, surrounded by a heavy fibrous stroma. Although all the coats are invaded, the growth is chiefly confined to the mucous and submucous layers. The protoplasm of the cells is pale and scanty, but the nuclei stain darkly. MacCarty describes the nuclei as generally oval or round with fewer irregularities than are presented by carcinomatous cells in other portions of the alimentary tract.

9. Graham, J. M.: Primary Cancer of the Vermiform Appendix, Edinburgh M. J. **10**:30-41, 1913.

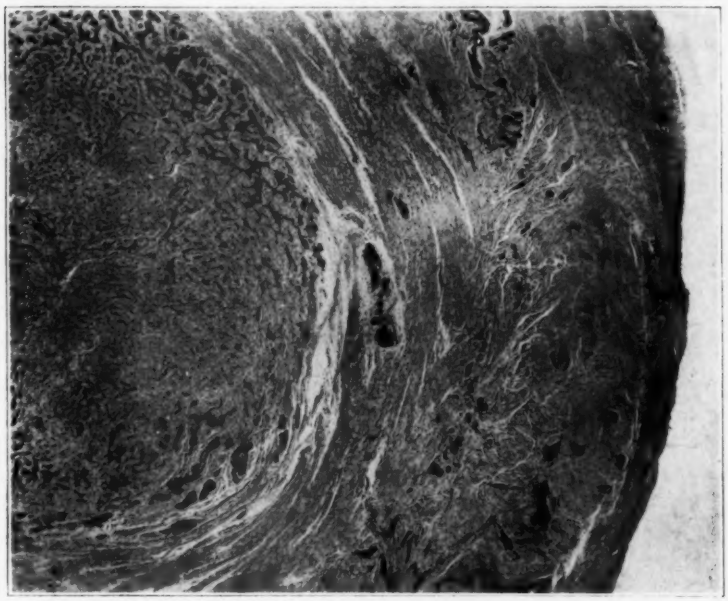

Fig. 4.—Involvement of all the coats of the appendix by carcinoma.

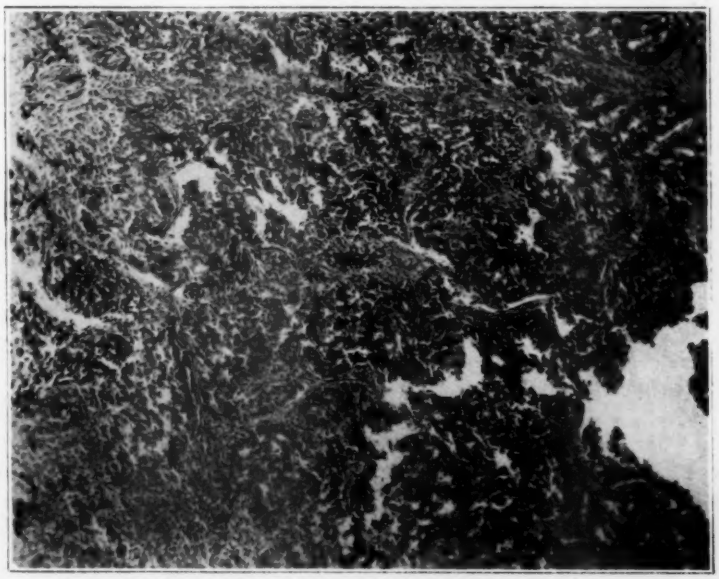

Fig. 5.—Irregular masses of epithelial cells closely packed in alveoli.

In this series of sixty-four cases, one specimen was diagnosed colloid carcinoma; the remainder may be classified in the so-called spheroidal group. Adenocarcinoma was not found.

The influence of chronic appendicitis as a factor in the production of carcinoma is evident from the appearance of the lumen and the number of twists and kinks in the region of the tumor. Graham states that it seems justifiable to conclude that in a certain number of cases the exciting cause of carcinoma may be found in the irritation of isolated tubules or of mucosa undergoing the process of obliteration. The effects of chronic lesions are evident in the production of gastric cancer and the same factors are probably effective in carcinoma of the appendix.

CONCLUSIONS

1. The prognosis following early removal of carcinoma of the appendix is more favorable than that for malignancy in any other part of the gastro-intestinal tract.

2. The appendix should be examined carefully in every laparotomy when possible and should be removed if any abnormality is present.

3. A preoperative diagnosis of carcinoma of the appendix is impossible because of the absence of distinguishing clinical signs.

4. A definite relationship exists between carcinoma of the appendix and chronic appendicitis. Obliterated appendixes should be carefully examined for signs of malignancy.

5. The relationship of cecal carcinoma to carcinoma of the appendix has not been proved.